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Dimethoate
Position Document 2/3

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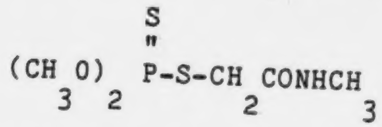
I. BACKGROUND

A. Introduction

(1) Chemical and Physical Characteristics

Dimethoate is an organophosphate insecticide and acaricide. Its chemical name is O,O-dimethyl S-(N-methylcarbamoylmethyl) phosphorodithioate.

Its chemical structure is:



$$(CH_3O)_2\overset{S}{\overset{\|}{P}}-S-CH_2CONHCH_3$$

Dimethoate is a white, crystalline solid with a camphorlike odor; the technical grade material is a yellow-brown liquid. The compound has a melting point of 51 to 52° C. It is most soluble in alcohols and ketones; its solubility in water is 2 to 3% (EPA 1977).

Dimethoate may be oxidized to a number of toxic products (cholinesterase inhibitors) by air, oxidative N-demethylation, and potassium permanganate. These toxic products include dimethoxon (dimethoate's oxygen analog), O,O-dimethyl S-(N-methylcarbamoylmethyl) thiophosphate, and both the N-demethylated analogs and the N-hydrox-methyl intermediates of dimethoate and dimethoxon. Dimethoxon, an important toxic metabolite of dimethoate, is formed when the sulfur in dimethoate is replaced by oxygen (EPA 1977).

(2) Registered Uses and Production

Dimethoate has been produced as a pesticide since 1963; it is a contact, residual and systemic insecticide/acaricide that is especially effective against rasping and sucking insect pests. It is available in emulsifiable concentrates, wettable powders, dusts and granules. Forty-seven registrants hold Federal registrations for 99 products, and 6 additional companies have applied for Federal registration. The most recent Agency records show that a total of 2,491,877 pounds of dimethoate were produced during 1976 (EPA 1979)

(3) Tolerances

Tolerances for total residues of dimethoate in or on raw agricultural commodities are listed in 40 CFR 180.204 as follow: 2 parts per million (ppm) in or on alfalfa, apples, beans (dry, lima, snap), broccoli, cabbage, cauliflower, celery, collards, endive (escarole), grapefruit, kale, lemons, lettuce, mustard greens, oranges, pears, peas, peppers, soybean forage, soybean hay, spinach, Swiss chard, tangerines, tomatoes, turnips (roots and tops), and wheat (green fodder and straw); 1 ppm in or on corn fodder and forage, grapes, and melons; 0.2 ppm in or on potatoes and sorghum forage; 0.1 ppm in or on cottonseed, pecans, safflower seed, and sorghum grain; 0.1 ppm (negligible residue) in or on corn grain; 0.05 ppm (negligible residue) in or on soybeans; 0.04 ppm (negligible residue) in or on wheat grain; 0.02 ppm (negligible residue) in eggs and in meat, fat, and meat byproducts of cattle, goats, hogs, horses, poultry, and sheep; and 0.002 ppm (negligible residue) in milk.

B. Applicable Sections of FIFRA

The Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136 *et seq.*) as amended, confers authority on EPA to regulate pesticide products. Section 3 (a) of the Act requires all pesticide products to be registered by the Administrator before they may be sold or distributed. Before the Administrator may register a pesticide, however, he must determine that its use will not result in "unreasonable adverse effects on the environment," defined in Section 2(bb) of FIFRA to mean "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide." In other words, any registration decision must take into account both risks and benefits from the pesticide's use.

Section 6(b) of FIFRA authorized the Administrator to issue a notice of intent to cancel the registration of a pesticide or to change its classification if it appears to him that the pesticide or its labeling "does not comply with the provisions of [FIFRA] or, when used in accordance with widespread and commonly recognized practice, generally causes unreasonable adverse effects on the environment." Thus, the Administrator may cancel the registration of a pesticide whenever he determines that it no longer satisfies the statutory standard for registration; this standard requires, among other things, that the pesticide "perform its intended function without unreasonable adverse effects on the environment" [FIFRA 3(c)(5)(C)]. He may also cancel the registration of a pesticide if its labeling also does not comply with the misbranding provisions of FIFRA which requires the labeling to contain certain language "adequate to protect health and the environment" (FIFRA 2(g)).

C. The "RPAR" Process

The Agency has designed a process, known as the Rebuttable Presumption Against Registration (RPAR) process, to gather risk and benefit information about pesticides which appear to pose adverse health or environmental effects. This process allows an open, balanced decision and invites participation by all interested groups.

This process is set forth in 40 CFR 162.11. These regulations describe various risk criteria and provide that an RPAR shall arise if the Agency determines that any of these criteria have been met. Once a rebuttable presumption has arisen, registrants, applicants, and interested persons may submit evidence in rebuttal or in support of the presumption. These people may also submit evidence on the economic, social, and environmental benefits of any use of the pesticide. If the presumptions of risk are not rebutted, the benefits evidence submitted is considered with the risk information. Various risk reduction methods and their costs are then analyzed. The Agency then determines whether the pesticide may be regulated so as to achieve a balance between risks and benefits. If the risks outweigh the benefits of use, the registrations for that use must be cancelled; conversely, if benefits exceed risk, registration will be continued.

D. Bases for the Rebuttable Presumption

The dimethoate RPAR notice cited three risk criteria which dimethoate had met or exceeded. [All such risk criteria are listed in the Code of Federal Regulations, 40 CFR Section 162.11(a)(3).] These three risk criteria were oncogenic effects in test animals, mutagenic effects (multi-test evidence) [40 CFR 162.11(a)(3)(ii)(A)], and reproductive and fetotoxic effects in test animals [40 CFR 162.11(a)(3)(ii)(B)].

In addition to these risk criteria, the RPAR notice listed two other possible adverse effects of dimethoate for which insufficient evidence existed to initiate a rebuttable presumption. The Agency requested registrants and other interested parties to submit data on these effects: delayed neurotoxicity and synergism of dimethoate by other pesticides.

E. Organization of Position Document

This Position Document contains six parts. Part I is this introductory section. Part II contains an evaluation of the potential risks of dimethoate. It includes descriptions of the relevant data on risks, exposure data, and the Agency's present risk assessment. Part III is a description of the potential economic benefits of dimethoate. Part IV describes the range of the regulatory options identified for the reduction of risks. Part V is the Agency's recommended option and a comparison of the regulatory options identified in Part IV. Finally, Part VI delineates additional testing requirements.

II. RISK ANALYSIS AND ASSESSMENT

A. Rebuttal Analysis

The Agency has received comments concerning the oncogenic, mutagenic, and reproductive and fetotoxic effects studies which were the basis for issuing a rebuttable presumption. The Agency has reviewed these studies again in the light of the rebuttal comments and has concluded that comments submitted to date fail to rebut the presumptions and that dimethoate continues to exceed the risk criteria outlined in 40 CFR Section 162.11 based on the chemical's ability to induce oncogenic, mutagenic, and reproductive and fetotoxic effects. Rebuttal comments received and the Agency's response to those comments are set forth below.

(1) Rebuttals Relating to the Presumption of Oncogenicity

The Agency received responses from five commentors on the oncogenicity risk criterion. The Agency's Carcinogen Assessment Group (CAG) has reviewed the rebuttals and additional information submitted (Memo 1978a). Based on this evaluation, the Agency has concluded that these rebuttals, taken individually, do not invalidate the oncogenicity risk criterion cited in the RPAR notice. However, based on a re-analysis of the studies involved and the rebuttal comments as a whole, the EPA Carcinogen Assessment Group has concluded that the weight of evidence for dimethoate's carcinogenicity is only suggestive, that the evidence warrants further studies, and that the evidence is inadequate to justify a quantitative assessment of cancer risk (Memo 1979g) [see also Section II.C].

The Agency cited three studies in its discussion of the possible oncogenic effects of dimethoate. The first study (Gibel et al. 1973) showed positive oncogenic effects. Ten-week-old Wistar rats of both sexes were administered doses of dimethoate, twice weekly by gavage, of 5, 15, and 30 mg/kg. One other group of animals was given 15 mg/kg intramuscularly. There was a significant increase of malignant tumors at 30 mg/kg (oral route) and 15 mg/kg (intramuscular route). In addition, there was a significant linear trend ($p<0.01$) for the oral route. The second study (NCI 1977) was negative for oncogenic effects. Osborne-Mendel rats of both sexes, 35 days old, were administered 250 and 125 ppm dimethoate in the diet. After 19 days, the doses were halved and continued for 61 weeks. The animals were observed for 115 weeks. Statistical analysis of tumor incidence by site and type showed neither an excess incidence of any specific tumor type nor any increase in total tumors. The third study (Steiglitz et al. 1974) indicated that dimethoate may cause hematotoxic effects in Wistar rats, including hyperplasia of the hematopoietic parenchyma in the bone marrow and extraosseous myeloid metaplasia. The Agency did not base its RPAR on this third study because the study lacked sufficient detail. However, the Agency requested registrants and other interested parties to submit to the Agency information on these, or similar, effects of dimethoate.

(a) Gibel et al. (1973)

(i) Source and Composition of Test Compound

Several commentors questioned the source of dimethoate used by Gibel et al. (1973), pointing out that the physical and chemical properties of Gibel's test material are different from those of dimethoate marketed in the U.S. (30000/16:#5A; #13; #25A; #35; #36).

The Agency has rejected these rebuttal attempts. The source of the material was the Bitterfeld Chemical Co. (Letter 1975). According to Dr. Gibel, the material was obtained from the Bitterfeld Co. and was recrystallized for use in the study. The recrystallized product was 99% pure, which implies that the crystallized product was similar in purity to that marketed in the U.S. (The Agency notes that the study by Lewerenz et al. (1970), which was submitted as a negative study for carcinogenicity by American Cyanamid Co. and Montedison USA, Inc., was also conducted with dimethoate obtained from the Bitterfeld Chemical Co. [see Section II.A.(1)(b)] for a discussion of the Lewerenz et. al. study.)

(ii) Abnormal Pattern of Mortality

Two commentors (30000/16:#5A, #13) pointed out that the Gibel et al. study does not show the normal pattern of mortality, because the high-dose group survived longer than the low-dose group.

The Agency has rejected this rebuttal attempt. The Agency acknowledges that mean survival time in days for each group in the Gibel et al. study appears to be inconsistent with normal toxicological responses, i.e., the high-dose group survived longer than the low-dose group. This pattern of mortality, however, has also been observed in other carcinogenic bioassay studies, including the NCI dimethoate study (NCI 1977). In the NCI dimethoate bioassay, both the high and low-dose male rats survived longer than the controls. The Agency concludes it is unlikely that differences between mean survival times of the high- and low-dose groups would account for the tumor incidences in the Gibel study.

(iii) Insufficient Data

American Cyanamid Co. (30000/16:#5A) and Menzer (30000/16:#35) pointed out that Gibel et al. did not report either the lifespan of individual animals or the sex of the animals in each dose group.

The Agency has rejected these rebuttal attempts. Gibel did not report individual survival days per animal but did report mean survival days for the controls versus each experimental group. These data permit evaluation of the test results. While the Agency would be interested in details of individual survival times, the study may be evaluated in terms of mean survival times.

The Gibel et al. study also did not distinguish between the number of animals of each sex in each dose group. While this is normally reported, the absence of this information does not negate the test results as reported.

(iv) Method of Administration

American Cyanamid Co. (30000/16:#5A) and Menzer (30000/16:#35) stated that Gibel used the gavage method to administer the chemical for his carcinogenesis study and concluded that this method of administration is not acceptable.

The Agency has rejected this rebuttal attempt. Gavage is an acceptable method for administration of chemical carcinogens in bioassays. The NCI frequently uses this method in their bioassay program. While Gibel has not made clear why this method was employed rather than the more commonly used method of dietary intake, the results of this study are not in question because of this route of administration, especially since the target organ was not the stomach. Since tumors were reported at remote sites, the test material was obviously absorbed and disseminated.

(v) Incorrect Dosage Data

American Cyanamid Co. (30000/16:#5A) indicated that Gibel reported dosage information incorrectly. The registrant stated that this represented a lack of organization in the research program and concluded that: (1) the Gibel study was poorly conceived; (2) it was executed in an inappropriate fashion; and (3) it resulted in data that are not scientifically useful or valid.

The Agency has rejected this rebuttal attempt. The dosage information incorrectly reported in Table 4 of Gibel's study does not by itself negate the significance of the study. Similar problems are apparent in the report by Lewerenz et al. (1970). For example, Lewerenz et al. reported that 75 ppm dimethoate in the diet was equal to 20 mg/kg per day. Data representing the average body weight and feed consumption, however, indicated a true dose level of 5.5 mg/kg per day in females and 5.88 mg/kg per day in males. Apparently, Lewerenz reported a dose four times higher than the data indicated.

(vi) Low Exposure from Food Residues

American Cyanamid Co. (30000/16:#5A) and Montedison USA, Inc. (30000/16:#25A) pointed out that, in two subsequent papers (Dedek et al. 1975 and Gibel et al. 1976), Gibel concluded that the hazard to consumers (resulting from dimethoate) "will probably not have to be expected in the future." The registrants also stated that, considering both the amount of dimethoate residues on agricultural crops and the legally established waiting periods between use of dimethoate and harvest, there is little or no danger of cancer formation.

The Agency has rejected these rebuttal attempts. The Agency is concerned about the hazard to the applicators of dimethoate as well as to the consumer exposed to dimethoate-treated commodities. Gibel stated that, in his opinion, exposure to dimethoate in food will not pose a cancer risk. The Agency notes, however, that Dr. Gibel expressed his real concern when discussing potential oncogenic risk to workers involved in the production and application of dimethoate. Dedek et al. (1975) stated, "The results of these studies should be taken into consideration in optimizing safety measures, both for pesticide production and agricultural workers handling pesticides." In a subsequent paper (Gibel et al. 1976), Gibel warned that "the groups of persons coming into direct contact with such pesticides as phosphoric acid esters (Dimethoate) - workers in production and in agriculture - must therefore be subjected to particularly careful preventive-medical control and must be held to very vigorous worker-protection guidelines."

(vii) Lack of Tumors in Controls

American Cyanamid (30000/16:#5A) and Montedison USA, Inc. (30000/16:#25A) indicated that it is extremely unusual that no malignant and very few benign tumors were found in the Wistar rat control group. The previous record of the Wistar rat group is not the low spontaneous tumor rate of 8.7% cited by Gibel. This gross difference could indicate that the control rats were not thoroughly examined. Additional tumors in the control animals would have radically altered their conclusions.

The Agency has rejected this rebuttal attempt. There is no indication in the experimental report that the controls were examined differently than the treated animals. Therefore, there is no basis for the statement. CAG was unable to identify and agree upon a spontaneous tumor rate for the Wistar rat since these rates seem to vary rather widely among different laboratories, depending upon the husbandry.

(b) New Study Offered in Rebuttal

American Cyanamid (30000/16:#5A) and Montedison USA, Inc. (30000/16:#25A) submitted an unpublished study by Lewerenz et al. (1970), which was reported as negative for carcinogenicity. The registrants pointed out that the same strain of rat was used in both the Lewerenz and Gibel papers and concluded that the Lewerenz study negates the positive findings by Gibel. The registrants also pointed out that the Lewerenz paper bridged the gap between the NCI (negative) and Gibel (positive) studies.

The Agency has rejected this rebuttal attempt. The source of the test material for both the Lewerenz et al. (1970) and Gibel et al. (1973) studies was the Bitterfeld Chemical Company. The same strain of rat (Wistar) was used in both studies, but the dose levels were substantially different. Lewerenz et al. (1970) used lower doses than did Gibel et al. (1973). Based on average body weight and feed consumption data presented, the male rats in the Lewerenz study were given 5.5 mg/kg per day and females were given 5.88 mg/kg per day in the highest dose group (75 ppm). Gibel, on the other hand, administered 30 mg/kg per day twice weekly. This difference in dose could account for the difference in response.

CAG (Memo 1978a) has reviewed the Lewerenz et al. (1970) data and found deficiencies in the pathology report, since only the results of macroscopic examinations are reported. The tumor sites are not specified, and it is therefore not possible to fully evaluate the pathology. CAG concludes that the Lewerenz study cannot be used to negate the result of Gibel et al. (1973) nor to confirm the negative NCI study.

(c) Steiglitz et al. (1974)

(i) Lack of Information

American Cyanamid Co. (30000/16:#5A) argued that Steiglitz et al. (1974) provided very little information or data about their study. Specifically, the registrant pointed out that it was unclear whether the percentage incidence of myeloproliferation and extra-osseous myeloid metaplasia referred to the total of all animals and all dosages or to one particular dosage; that no mention was made of control animals; that leucocyte counts were compared to unspecified control animals; and that the authors did not indicate when leucocyte counts were made.

The Agency has rejected this rebuttal attempt. The papers by Steiglitz et al. (1974) and Gibel et al. (1973) were based on a single experiment. The Steiglitz et al. (1974) paper addressed the effect observed on the blood and blood forming tissues while Gibel et al. (1973) addressed the oncogenic effects of dimethoate. The controls for both papers (Gibel et al. (1973) and Stieglitz et al. 1974) are described in Gibel et al. (1973). Furthermore, the judgement of the frequency of myeloproliferation and extra-osseous myeloid metaplasia is subjective and may not require a control group. The Agency acknowledges, however, that additional information concerning the control group would have made the study more definitive. Although the authors did not indicate when leucocyte counts were made, the count was in the normal range for controls but was high in the treated group.

(ii) Source of Test Compound

The Calif. Dept. of Food and Agriculture (30000/16:#36) commented that the compound used in this study was probably the same as that used by Gibel et al. (1973).

The Agency notes that both Steiglitz et al. (1974) and Gibel et al. (1973) reported on the same group of test animals. Gibel reported on carcinogenic effects, Steiglitz on hematological effects. The test compound was the same for both papers (Letter 1975).

In summary, the comments submitted on the oncogenic risk criterion do not rebut the Agency's original presumption concerning the oncogenic potential of dimethoate. The Gibel et al. study as reported in 1973 and subsequent information submitted by Dr. Gibel (Letter 1975) still leave out many details regarding the conduct of this study that the Agency would be interested in reviewing. CAG has concluded, however, that the available data are only suggestive of oncogenicity (Memo 1979g). The Agency's discussion of oncogenic risk from dimethoate is contained in Section II.C.

(2) Rebuttals Relating to the Presumption of Reproductive and Fetotoxic Effects

The Agency received comments from five commentors on the reproductive and fetotoxic risk criterion. The Agency has reviewed the rebuttals and additional information submitted (Memo 1978b). Based on this evaluation, the Agency has concluded that these rebuttals do not invalidate the three studies cited in the RPAR notice.

Budreau and Singh (1973) studied the effect of zero and 60 ppm of dimethoate in the drinking water of five generations of CD-1 mice. The 1973 Budreau and Singh paper is based on the more detailed thesis by Budreau (1972). Dimethoate treatment significantly altered reproductive performance, as indicated by reduced mating success and longer reproduction time. In all generations, dimethoate-treated females required significantly longer periods than the controls to produce first litters, and second litter mating success ranged from 33 to 61% ($p<0.01$) of the control values. Although litter size and weight were not reduced at birth, the survival rate of the total pups and litters was significantly ($p<0.01$) reduced by dimethoate treatment in generations I, III, IV, and V. The highest rate of mortality occurred in the first postnatal week. The major flaw with the Budreau and Singh (1973) study is the lack of multiple dose levels on which to base dose-response relationships.

Scheufler (1975a) observed a significant increase in the number of dead embryos ($p<0.01$) on the ninth day of pregnancy following administration of a single 40 mg/kg dose of dimethoate intraperitoneally to female AB Jena-Halle mice on the day of conception. The daily injection of dimethoate at 40 mg/kg during the first 14 days of pregnancy resulted in the death of four times as many implanted embryos as the controls for this strain. The administration of 25 mg/kg of dimethoate intraperitoneally to female C57BL mice increased the number of non-pregnant females to 70% compared to the 20-30% control value. Likewise, for DBA mice, a dose of 20 mg/kg for 14 days resulted in the absence of embryos in 50% of the treated females. The usefulness of this study for risk extrapolation is limited due to the route of administration. A lack of reported data makes statistical interpretation difficult.

American Cyanamid Co. (1965) conducted a three generation feeding study with CF1 strain albino mice, using 0, 5, 15, and 50 ppm of dimethoate in the diet. The report concluded that "reproduction and lactation performance was good for all groups." A review of the data by an EPA scientist indicated that at 50 ppm, there was an effect, albeit not statistically significant, on litter survival (Courtney 1977).

(a) Rebuttals Relating to More Than One Study

(i) Type of Effects Observed

American Cyanamid Co. (30000/16:#5A) defined fetotoxicity as the failure of the fetus to survive through the entire gestation process and pointed out that neither the five generation study of Budreau (1972)[1], nor Budreau and Singh (1973), nor the three generation study of American Cyanamid Co. (1965) demonstrated any such effect.

The Agency has rejected this rebuttal attempt. Although the commentor's definition is very narrow, Cyanamid is correct in stating that neither Budreau (1972), Budreau and Singh (1973), nor American Cyananid Company (1975) observed evidence of toxic damage to the fetus. Budreau (1972) and Budreau and Singh (1973) did report an increase in neonatal mortality. This is a postnatal toxicity effect, as opposed to a fetotoxic effect. Since the RPAR notice cited general reproductive (as well as fetotoxic) effects, the Agency's original presumption of risk remains. The Agency also points out that the Scheufler study did display an increase in fetal mortality, or fetotoxicity.

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[1] Budreau (1972) is a doctoral thesis upon which the publication of Budreau and Singh (1973) is based. The thesis was not cited in the RPAR notice.

(b) Budreau and Singh (1973)

(i) Inconsistent Data

American Cyanamid Co. (30000/16:#5A) argued that the Budreau and Singh data are suspect because the data from Budreau (1972) is expressed not as survival percentages [like the data in Budreau and Singh (1973)] but as the percent mortality of pups or litters. The registrant argued that in every instance the percentage of survival given by Budreau and Singh (1973) was nearly 20% lower than that which could be calculated from Budreau (1972). The registrant stated that this difference is large enough to change the survival rate differences, from insignificant in the thesis to significant in the publication.

The Agency has rejected this rebuttal attempt. It appears that, in the thesis and report, the "n" value (number of pups surviving) was adjusted to consider only the living pups; litters with 100% mortality were not considered. There is no inconsistency between the data given in the paper and in the thesis and no reason to view these data as suspect.

(ii) Drowning of Litters

American Cyanamid Co. (30000/16:#5A) stated that lost litters, which were attributed to the effects of dimethoate, were actually caused by drowning of entire litters by water leaking into the plastic cages from the watering bottles.

The Agency has rejected this rebuttal attempt. On page 103 of the thesis (Budreau 1972), last paragraph, the author states, "Mortality among adult animals varied from 4% for the fenthion group and 8% for the dimethoate and control groups. A main factor in the mortality was swamping of some cages by a bottle that inadvertently opened...no mortality could be directly attributed to the diet." The quoted statement was the only reference in the thesis to death by drowning. The Agency notes that the author stated that the deaths were of adult animals; no litters were subject to drowning. Since an equivalent percentage of deaths occurred in the dimethoate and control groups from this accidental cause, these animals can be deleted from consideration without impairing the study.

(iii) Dam Transfer Experiment

American Cyanamid Co. (30000/16:#5A) commented that the dam transfer experiment, which indicated that the pups may have died because of pesticide residue in the milk, was not performed with dimethoate but with fenthion.

The Agency has accepted this rebuttal attempt. The Agency improperly interpreted this portion of the study.

(iv) Contaminated Drinking Water

American Cyanamid Co. (30000/16:#5A) also contended that another possible cause of mortality would be from the pups drinking the water containing dimethoate directly, thus exposing themselves to very high dosages of dimethoate on a body weight basis. The Agency has rejected this rebuttal attempt. There is no evidence to support this contention.

(v) Nutritional Difficulties

American Cyanamid Co. (30000/16:#5A) also argued that litter mortality was attributable to factors other than dimethoate treatment, such as nutritional difficulties. The Agency has rejected this rebuttal attempt. There was no evidence of nutritional difficulties in either the adults or pups at birth. On the contrary, litter size or weight at birth were not reduced, but pup mortality did increase significantly with dimethoate treatment.

(vi) Lowered Mating Success

American Cyanamid Co. (30000/16:#5A) also stated that Budreau and Singh (1973) could not identify why the mating success of dimethoate-treated animals was lower than that of the controls. The Agency has rejected this rebuttal attempt. Budreau and Singh (1973) clearly attributed the lowered mating success to dimethoate treatment, but were unable to pinpoint the exact mechanism of action, or target organ, for the compound.

(vii) Condition of Test Animals

American Cyanamid Co. (30000/16:#5A) further questioned the validity of the study because of the condition of the animals used. The registrant cited a 25% decrease in weight for dimethoate-treated animals in an experiment described by the chart on page 73 in Budreau (1972). The registrant also cited the "lethargic" condition of the test animals as affecting mating success.

The Agency has rejected the first part of this rebuttal attempt. The data on decreased weight refer to a preliminary experiment in which the animals were housed singly, and in which there was a great weight loss and a concomitant lack of reproduction. In the 1973 paper, however, the studies were performed on mice housed in groups of 4 to 6 in plastic cages, a condition found to be optimal as a result of the preliminary studies detailed in the thesis. The authors noted a minimal effect on weight gain only in the first two weeks of treatment, and no increase in mortality among the adults. The lethargic condition of the males, which the registrant suggested as a reason for the effect on mating success, could very well be the result of the toxicological effects of dimethoate. The difficulty in separating toxic effects from adverse reproductive effects is one of the flaws in the study.

(viii) Selection of Test Animals

American Cyanamid Co. (30000/16:#5A) contended that neither Budreau (1972) nor Budreau and Singh (1973) included a description of the process for selecting test animals and argued that anything less than a completely random selection process could severely bias the results for all generations.

The Agency has rejected this rebuttal attempt. On page 30 of Budreau and Singh (1973), the authors state that the animals were randomly paired; on page 31, they state that matings were performed at random for all generations. There is no evidence that the selection procedure was anything less than a completely random process.

(ix) Definition of "Reproduction Time"

American Cyanamid Co. (30000/16:#5A) stated that the term "reproduction time" was used inaccurately. The Agency has rejected this rebuttal attempt. The term was used in accordance with the definition, given on page 81 of Budreau (1972), that reproduction time is "the number of elapsed days from the first day when the female was presented to the male to the day of delivery"; this would include time for impregnation to occur. Although, as American Cyanamid correctly pointed out, the reproduction time was significantly different for dimethoate-treated animals only for the first litter, the lowered mating success (33 to 61% of control value) for second litter production may have masked a longer reproduction time for the second litters.

(x) Maternal Toxicity

Montedison USA, Inc. (30000/16:#25A) stated that no teratogenic effects were observed in the Budreau and Singh study, and that the effects observed, namely, lower mating success, longer reproduction time, and reduced survival and growth rates, were to be expected in severely intoxicated females.

The Agency has rejected this rebuttal attempt. Since the dosage of dimethoate used did not increase mortality among the adults, and produced a small diminution of weight gain only in the first two weeks of treatment, there is no basis for attributing the adverse effects to maternal toxicity.

(xi) Incorrect Dosage Data

Menzer (30000/16:#35) commented that the estimate of water consumption made by Budreau and Singh (1973) was unrealistic, since the stated daily dosage of 9.5 to 10.5 mg dimethoate/kg would indicate that the mice drank only 4 ml. of the dimethoate-treated water per day. The commentor suggested that a more realistic estimate of water consumption would be 12 to 15 ml. of water per day, resulting in a daily dosage of dimethoate between 36 and 45 mg/kg rather than 10 mg/kg. American Cyanamid Co. (30000/16:#5A) also noted that the actual dosage given to the mice in the study was probably closer to 36-45 mg/kg.

The Agency has rejected this rebuttal attempt. The Agency has concluded that the Budreau estimate of 10 mg/kg/day is a reasonable estimate of the dose level, since pregnant mice drink an average of 8.8 ± 0.5 ml. of water per mouse per day (Memo 1978b; Letter 1978); there was no difference in water consumption at the beginning of gestation compared to the end of gestation. At a dose level of 60 ppm in the drinking water, 8.8 ml. of water in a 36 gram mouse would be a dose of 13.6 mg/kg, which is quite close to the dose of 10 mg/kg calculated by Budreau.

(xii) Effect on Neuro and Endocrine Systems

The California Dept. of Food and Agriculture (30000/16:#36) commented that the study by Budreau and Singh (1973) indicated that dimethoate significantly reduced mating success and increased reproduction time but argued that since the studies dealt primarily with end effects, the authors should have measured the effect of dimethoate on functioning neuro and endocrine systems.

The Agency has rejected this rebuttal attempt. The Agency agrees that studies of the mechanism of action of dimethoate would be of interest but concludes that the lack of such information does not affect the validity of the adverse reproductive effects demonstrated by the Budreau and Singh study.

(c) Scheufler (1975a)

(i) Lack of Detail

American Cyanamid Co. (30000/16:#5A) argued that Scheufler (1975a) was extremely abbreviated and lacked detail. The registrant cited the following specific examples: 1) although the number of corpora lutea, living and dead fetuses, dead embryos, and weights of the fetuses are said to have been recorded, these data are absent in the article; 2) it is not clear from the article whether the controls were concurrent; and 3) the table in the article indicates "total loss," but does not explain specifically what was lost (fetuses, experimental animals, "nuclei," or something else not mentioned). The registrant concluded that the absence of other significant data prevents statistical interpretation of the study.

The Agency has rejected most of these rebuttal attempts. These rebuttal points apparently stem, in part, from difficulties with the Agency's first translation of the German text (Scheufler 1975a). Although a comparison of this translation with the original article clarifies these rebuttals, the Agency nevertheless had the article translated a second time (Scheufler 1975b). On the first rebuttal point, the Agency agrees that these data were not provided in the article; the Agency points out, however, that these data were used to determine the pre-implantation, post-implantation, and total losses of embryos. The data on these losses were provided in the first translation. On the second point, the Agency agrees that the first translation is unclear on the concurrence of controls. The second translation (Scheufler 1975b) states, "Controls were also carried through with all experiments in the same time period...." The German text is equally clear on this point: "Zu allen Versuchen wurden im gleichen Zeitraum Kontrollen durchgefuhrt...." On the third point, the second translation also makes clear that the "total losses" are the pre- and post-implantation embryo/fetal losses. Because the pre-implantation loss was an "unreliable measurement value" (Scheufler 1975b), the author relied primarily on the post-implantation loss to describe embryotoxic effects. The comparison of post-implantation embryo loss with control values allows statistical interpretation of the study.

(ii) Definition of "Nuclei"

American Cyanamid Co. (30000/16:#5A) stated that the author [translator(?)] refers to "nuclei" as having been lost but does not define nuclei. The Agency points out that this term is often used by translators in referring to embryos or fetuses (Memo 1978b).

(iii) Total Loss Data

American Cyanamid Co. (30000/16:#5A) quoted the first translation that total loss was calculated "by assertion." The registrant also noted that the author stated he could not use the pre-implantation data.

The Agency has rejected this rebuttal attempt. The sentence referred to by the registrant, in the first translation (Scheufler 1975a), reads: "The preimplantary loss proved to be an unreliable measurement data after several experiments, whereby concurrently the data for the total loss was reduced by assertion." The same sentence in the second translation (Scheufler 1975b) reads: "The pre-implantation loss proved in several experiments to be an unreliable measurement value; this also limits the definitive significance of the total loss." It is clear, therefore, that the author did not calculate total loss "by assertion." As already noted, the "total loss" refers to pre-implantation and post-implantation loss of embryos [see Section II.A.(2)(c)(i)]. Since pre-implantation loss data were unreliable, the value of the "total loss" (as a measurement of embryotoxicity) was also reduced ["concurrently the data for total loss was reduced by assertion"]. The author relied on post-implantation loss to describe embryotoxic effects.

(iv) Route of Exposure

American Cyanamid Co. (30000/16:#5A) also argued that injecting dimethoate intraperitoneally was an entirely inappropriate route of exposure. The Agency has rejected this rebuttal attempt. Many investigators use this route of administration in teratology or perinatal toxicity studies; the information gained cannot be dismissed as unscientific or useless. The Agency would agree, however, that data obtained from studies utilizing the oral route of administration would be preferable when analyzing potential human risk.

(d) Exposure Rebuttals

Several commentors (30000/16:#5A, #13, #35, #36) indicated that the Agency incorrectly estimated oral exposure to dimethoate (i.e., through food) in that all food crops for which dimethoate is registered are not actually treated with dimethoate.

The Agency accepts this rebuttal comment. The Agency has revised its estimates of oral exposure to take into consideration data submitted by commentors, including USDA, concerning the percent of those crops actually treated with dimethoate [see Section II.B(4)]. Because of a lack of data concerning actual dimethoate residues on foods at harvest, the Agency assumes residues to be present at tolerance levels.

Several commentors (30000/16:#5A, #13, #25, #35, #36) submitted information concerning anticipated dermal exposure and indicated that the Agency overestimated dermal exposure.

The Agency accepts these rebuttal comments. The Agency has revised its estimates of dermal exposure to take into consideration comments and other data submitted [see Section II.B].

(c) Calculation of Margin of Safety

One commentor (30000:#16) criticized the manner in which the Agency calculated the margin of safety (MOS) for reproductive and fetotoxic effects. The MOS was derived by dividing the dosage which produced no observable effect in test animals by estimated total daily human exposure. The Agency's human exposure analysis was calculated assuming that the applicator would become soaked with dimethoate during application of the pesticide). The commentor indicated that it is only marginally conceivable that a young female applicator could be exposed (dermally) to dimethoate in this manner but that it is impossible to accept the premise that this event would take place daily through puberty, pregnancy and lactation, as it was received by the experimental animals.

The Agency has concluded that this rebuttal attempt is partially successful. The Agency based its rebuttable presumption for reproductive and fetotoxic effects upon the study by Budreau and Singh (1973), a multigeneration feeding study. The commentor's point that a young woman might be exposed to dimethoate only once or twice a year and that this exposure is quite different from continual daily exposure is well taken. However, new teratogenic data unavailable when the RPAR was issued has been submitted by Khera [unpublished, see section II.C(3)(a)].

Teratogenic studies such as those done by Khera (unpublished) involve dosing a pregnant animal during the critical periods of gestation, to determine if a teratogenic or fetotoxic effect can be demonstrated. Because the critical day of gestation, when any particular pesticide may expect an effect is not known, multiple doses are given for several days. The study by Khera (unpublished), therefore, is actually a series of acute daily doses and can be used as the basis for calculating the MOS for teratogenic effects.

Duration of exposure may play an important role in reproductive effects such as those observed by Budreau and Singh (i.e., increased generation time, decreased litter size, etc.). When teratogenic effects (Khera) are observed, the potential exposure during the critical days of gestation is the focus of concern.

(3) Rebuttals Relating to the Presumption of Mutagenicity

The Agency received responses from five commentors on the mutagenicity risk criterion. The Agency has reviewed the rebuttals and additional information submitted (Memo 1978d). Based on this evaluation, the Agency has concluded that these rebuttals do not invalidate the presumption of mutagenicity risk. No evidence has been presented to invalidate positive results in reverse mutation assays with *E. coli* WP2 UvrA and WP67 (Hanna and Dyer 1975), as well as with one forward mutation assay with *E. coli* K-12 (Mohn 1973). A dominant-lethal effect was reported, by Gerstengarbe (1975) in mice, but weaknesses were pointed out in the protocol which make quantifying the mutagenic potential difficult. Some of the rebuttals concerned the relative potency of dimethoate; this issue will be considered in assessing risk (see Section II.C). The Agency has accepted a rebuttal against the use of plant tests cited in the RPAR notice (because of the lack of control values for the Agarwal et al. (1973) study and the uncertainty about the heritability of effects reported in the Amer and Farah (1974) study. The Agency cited nine studies in the RPAR notice, which are listed in Table 1.

Table 1
Mutagenicity Studies Cited in Position Document 1

Rebuttal Reference	Study Type	Species & Strain	Doses	Results
Fahrig 1973	Induction of mitotic gene conversions	Saccharomyces cerevisiae D4	7 dose levels; 40 to 100 mM	positive response; significant dose-response
Hanna & Dyer 1975	Bacterial systems	Eschericia coli, WP2 uvrA and WP67; other E. coli & Salmonella typhimurium strains	5 to 10 ul	positive in E. coli WP2 uvrA & WP67; negative in other strains
Mohn 1973	Bacterial system	E. coli, K-12/gal1Rs18	5 dose levels; 1 to 6X10^{-3} M	positive response; significant dose-response
American Cyanamid Co. 1977	Metabolic-activation with rat liver enzymes	S. typhimurium and E. coli strains	20 to 100 ug/plate	no mutagenic response
Shirasu et al. 1976	Bacterial systems	Bacillus subtilis H17 Rec+ and R45-	not given	no mutagenic response
Agarwal et al. 1973	Cytology Study	bean (Phaseolus vulgaris)	0.1 & 0.5% spray at bud initiation	chromosomal abnormalities, including fragments, stickiness, & anaphase bridge formation
Amer and Farah 1974	Cytology	cotton (Gossypium barbadense) and bean (P. vulgaris)	both pure and formulated dimethoate at various dilutions	positive mutagenic response
Gerstengarbe 1975	Dominant-lethal	male mice (Mus musculus) AB Jena-Halle	single 80 mg/kg or 6.66 mg/kg daily for 30 days	positive mutagenic response
Bhunya and Behera 1975	Bone marrow cytology	male and female, mice (M. musculus)	injection of 1 cc/100 g body weight	centromeric fission and stretching

(a) Rebuttals Relating to More Than One Study

(i) Purity of Test Compound

Montedison USA, Inc. (30000/16:#25A) indicated that there were several contradictory findings among the submammalian mutagenicity tests and that this may be due to the uncertain purity of the dimethoate used.

The Agency has rejected this rebuttal attempt. The contradictory findings (i.e. there were positive as well as negative results) can be explained by means other than uncertainty about the purity of the test compound. The study by American Cyanamid Co. (1977) [see Section II.A.(3)(j)(i)], which was submitted as a study showing non-mutagenic effects, was actually positive and supported Hanna and Dyer (1975), which showed positive mutagenic activity in the same test strain.

(ii) Diverse Test Results

Hutton (30000/16:#13) argued that the "highly diverse lot of studies" presented in the mutagenicity section of Position Document 1 could justify any conclusion one wished to draw.

The Agency has rejected this rebuttal attempt. Mutagenic agents rarely show positive responses in all types of tests because the test results are subject to differences in the sensitivity of the test system, differences in absorption and metabolism, etc. The positive responses observed dictate that the Agency's concern is prudent in light of the potential human health risks.

(iii) Dosage Levels

Hutton (30000/16:#13) argued that test protocols (none specified by commentor) used incredibly large dosages that bear no relationship to the real world.

The Agency has rejected this rebuttal attempt. In order to detect the relatively low probabilities of mutations caused by the concentrations of chemicals found in the real world, it would be necessary to use large numbers of test subjects over a long period of time. This is impractical. It is scientifically acceptable, and even necessary, to use large dosages administered to a smaller sample of test subjects over a shorter span of time to magnify mutagenic effects to a statistically detectable level.

(iv) Bacterial Assays: Variable Results

The California Department of Food and Agriculture (30000/16:#36) argued that the introduction of a host of variables into the bacterial tests cited in the RPAR notice made interpretation of the results difficult. The commentor cited the conflicting results of American Cyanamid Co. (1977) and Mohn (1973) and suggested that the difference in response could be due to the metabolism of dimethoate by the microsomal liver fraction. The commentor also questioned the source of dimethoate and its manner of incorporation into the agar plate in Mohn (1973). The commentor argued that the results suggest either that dimethoate was not absorbed by the microorganisms, that it was no longer present as dimethoate, or that the concentration was too low.

The Agency has rejected these comments. American Cyanamid Co. (1977) has resolved the apparent difference in results [see Section II.A.(3)(j)(i)]. E. coli WP2 UvrA responds to dimethoate, but only at relatively high concentrations (Hanna and Dyer 1975; American Cyanamid Co. 1977). E. coli WP67, which differs from E. coli WP2 UvrA only in lack of polymerase A, was also positive [tested only by Hanna and Dyer (1975)]. Tests with S. typhimurium were negative except for strain TA-100 (a very sensitive derivative of TA-1535), which showed a dose-response suggestive of mutagenic activity (American Cyanamid Co. 1977). Unfortunately, the TA-100 had a very high background of mutational frequency (230 to 522 colonies/plate), which reduced the response. Normal rates should be about 160 colonies/plate (De Serres and Shelby, 1979). In addition, another strain of E. coli was positive in a forward mutation assay (Mohn 1973). These results, therefore, are consistent with other studies demonstrating a low potency mutagen, active by means of base substitution.

(b) Hanna and Dyer (1975)

(i) Control Plates

American Cyanamid Co. (30000/16:#5A) indicated that the authors did not use, or failed to report, the results from negative and positive control plates.

The Agency has rejected this rebuttal attempt. The study reported many negative responses among the chemicals tested as well as positive responses for known mutagens, e.g., trimethyl phosphate. These responses are adequate to demonstrate the proper operation of the system used by Hanna and Dyer, especially since their results with dimethoate were confirmed by American Cyanamid.

(ii) Dose Not Reported

American Cyanamid Co. (30000/16:#5A) pointed out that, since the authors did not state the dose used, a dose-response relationship could not be calculated in a statistical analysis.

The Agency has rejected this rebuttal attempt. The Hanna and Dyer (1975) study is a spot test for mutagenicity and is not a quantitative test. In this context, dose is not relevant to the determination of mutagenic potential.

(iii) Incorrect Protocol

American Cyanamid Co. (30000/16:#5A) stated that the protocol used was incorrect because the incubation period was extended one additional day and because, when the study was performed with the correct incubation period, the results were negative rather than positive.

The Agency has rejected this rebuttal attempt. The protocol was developed by Bridges et al. (1972) who incubated their plates for two days. It is standard protocol (De Serres and Shelby, 1979), however, to look for slow-growing revertant colonies at 72 hours. Negative results with other compounds tested by Hanna and Dyer (1975) indicate that no extraneous influences were introduced by this extension.

(iv) Toxicity Estimate

American Cyanamid Co. (30000/16:#5) stated that the determination of toxicity for this study was inadequate. Toxicity "was estimated only by noting a reduction in the number of revertants relative to negative controls."

The Agency has rejected this rebuttal attempt. The toxic effect would only reduce the number of prototrophic revertants. A positive test result is still valid in a spot test because the growth of colonies due to endogenous histidine being released from killed cells would be distributed throughout the plate and would not be concentrated in the center of the plate where the dimethoate was placed.

(v) Confirmation of Phenotypes

American Cyanamid Co. (30000/16:#5A) indicated that colonies which appeared to be revertants were not purified and retested on minimal plates to confirm their phenotypes.

The Agency has rejected this rebuttal attempt. The procedure outlined by the registrant is very time consuming and expensive; it is also superfluous in a screening examination such as this spot test.

(c) Shirasu et al. (1976)

American Cyanamid Co. (30000/16:#5A) indicated that this study supports the contention that dimethoate is not mutagenic.

The Agency agrees that this study did not show dimethoate to be mutagenic; this study, however, does not rebut the presumption that dimethoate can act as a mutagen. The test protocol used by Shirasu et al. (1976), which resulted in a negative mutagenic response, is different from those test protocols showing positive results (Hanna and Dyer 1975). Shirasu et al. (1976) used a different inoculum (0.02 ml of a 1 mg/ml solution on a paper disc) and incubated test plates for two days. Hanna and Dyer (1975) used "a crystal or 5-10 ul" of chemical placed directly onto the plates, which were incubated for three days. These tests, therefore, do not necessarily contradict one another. The differences in method preclude direct comparison of the positive and negative test results. The Agency notes that positive results were observed in a spot test with the same strain of _E. coli_ [American Cyanamid Co. 1977] using dimethoate at a concentration of 10,000 ug/disc [see Section II.A.(3)(j)(i)].

(d) Mohn (1973)

(i) Invalid Test System

American Cyanamid Co. (30000/16:#5A) stated that the testing system used in the Mohn (1973) study has not been used widely enough to allow validation of its results.

The Agency has rejected this rebuttal attempt. The 5-methyl tryptophan resistance mutation system used by Mohn (1973) has been adequately studied, and the test was performed with proper protocols to indicate valid mutations.

(ii) Low Potency of Compound

American Cyanamid Co. (30000/16:5A) indicated that known mutagens, such as MNNG, were over 10,000 times more potent than dimethoate in this test system.

The Agency has rejected this rebuttal attempt. The potency of dimethoate is much less than MNNG in this system; however, a proper dose-response curve at a non-toxic level was demonstrated for dimethoate, indicating mutagenic activity.

(iii) Liquid Suspension Assay

American Cyanamid Co. (30000/16:#5A) indicated that liquid suspension tests such as those used by Mohn (1973) can give results which conflict with plate tests, depending on the compound being tested (Ames et al. 1975).

The Agency has rejected this rebuttal attempt. The statement is misleading since Ames noted (Ames et al. 1975) that liquid suspension tests were usually less sensitive than plate tests. Ames also noted that the liquid suspension test identified two mutagens that were not picked up with the plate incubation system. Use of the liquid suspension system does not make a test less valid.

(e) Agarwal et al. (1973)

(i) Phytotoxicity of Dimethoate

Montedison USA, Inc. (30000/16:#25A) argued that mutagenicity tests on plants could be questionable, owing to the well-known phytotoxicity of dimethoate beyond a certain level of concentration in the plant tissues.

The Agency has rejected this rebuttal attempt. One of the criteria for dose selection in mutagenicity tests is that toxicity be demonstrated at the high dose level. Both plant studies reported a partial toxic effect at the higher levels.

(ii) Lack of Controls

American Cyanamid Co. (30000/16:#5A) pointed out that no controls were reported.

The Agency agrees that this is a valid criticism and that this study is not acceptable as primary evidence for the mutagenicity of dimethoate due to the absence of reported controls. The increase in chromosomal fragmentation and bridge formation, however, suggests that dimethoate may produce cytogenetic effects for *Phaseolus vulgaris*.

(iii) Variation in Results

American Cyanamid Co. (30000/16:#5A) indicated that the experiment was apparently repeated with variation in results.

The Agency has rejected this rebuttal attempt. There is nothing in the paper which indicates that the experiment was repeated. The chromosomal abnormalities, however, were scored at both metaphase and anaphase, and thus a variation in numbers could be expected.

(f) Amer and Farah (1974)

As previously noted [see Section II.A (3)(e)(i)], the Agency has rejected a rebuttal against the use of plant tests to demonstrate dimethoate's mutagenicity because of dimethoate's phytotoxicity.

(i) Lack of Control Data and Analyses of Results

American Cyanamid Co. (30000/16:5A) pointed out that neither control data nor descriptions or analyses of the abnormalities were given.

The Agency has rejected this rebuttal response. Although no control data were given, an unmistakable dose-response curve was obtained for the root treatment data. Photographs were furnished to describe the abnormalities.

(ii) Non-Heritable Abnormalities

American Cyanamid Co. (30000/16:#5A) cited a later study by the authors (Amer and Farah 1976) which indicated that the reduction in the mitotic index and the abnormal mitoses (Amer and Farah 1974) were not heritable or permanent events and that the chromosome fragmentation was not necessarily evidence of mutation.

The Agency has accepted this rebuttal response. The papers were concerned with cytological effects and the majority of the effects reported were probably non-heritable cytotoxic disturbances of the spindle apparatus. Evidently no attempt was made to score mutagenic aberrations. Furthermore, the authors noted that most of the observed bridges were sticky bridges. These sticky bridges may not be a mutagenic response.

(iii) Differences Between Pure and Formulated Dimethoate

American Cyanamid Co. (30000/16:#5A) argued that wide differences were noted between pure and formulated dimethoate. Pure dimethoate was cited as causing greater abnormalities than the formulated product when applied as a seed soak while the reverse was noted when applied to root tips.

The Agency has rejected this rebuttal attempt. Since treatment with pure dimethoate (as compared to formulated dimethoate) greatly decreased the number of dividing cells and the mitotic index when applied to root tips but not when applied as a seed soak, the differences probably reflect a toxic effect and do not invalidate the results.

(iv) Procedural Errors

American Cyanamid Co. (30000/16:#5A) indicated that various procedural points should have been followed, as recommended by Cohn and Hirschhorn (1971).

The Agency has rejected this rebuttal attempt. Cohn and Hirschhorn (1971), the reference presented by the registrant, did not contain any information on protocol as indicated by American Cyanamid's rebuttal submission. Methods are not well established for many of these studies, and results must be interpreted on an individual basis.

(g) Fahrig (1973)

(i) Lack of Survival Data

American Cyanamid Co. (30000/16:#5A) indicated that no survival data were given in order to interpret the results correctly.

The Agency has rejected this rebuttal attempt. Detailed survival kinetics would be desirable, but the paper does state that the inactivation ("inaktivierung") of *Saccharomyces* shows a strong increase or is uniformly strong as soon as a certain concentration threshold (85 mM) is exceeded. Since the linear dose-response curve for dimethoate was measured below this threshold, the results are acceptable.

(ii) Lack of Detail

American Cyanamid Co. (30000/16:#5A) indicated that no record of background mutations, no negative controls, no details on termination of the experiment, no information on size of the test population, and no identification of the solvents used were given.

The Agency has rejected this rebuttal attempt. Many experimental details were not reported in the paper as published, but the positive control, methylmethansulfonate, and the four organo-phosphorus insecticides produced well-defined, linear, dose-response curves. There is no evidence to suggest the lack of proper protocol.

(iii) Improper Handling of Test Colonies

American Cyanamid Co. (30000/16:#5A) indicated that no precautions were taken to prevent colonies, which phenotypically resemble gene conversions, from arising through sporulation and meiosis.

The Agency has rejected this rebuttal attempt. Five hours of treatment should not have induced sufficient sporulation to alter the results, particularily in view of the excellent dose-response curves obtained. Moreover, the reference cited by the registrant (Zimmerman 1975), which was the basis for the rebuttal, in fact states that storage in buffers for more than six hours should be avoided. Fahrig (1973) treated colonies for only five hours.

(h) Gerstengarbe (1975)

(i) Improper Controls

American Cyanamid Co. (30000/16:#5A) indicated that identical negative controls were used in Experiments 1, 2, and 4 despite their different experimental design and their different time frames; no positive controls were used; and only one dose was administered, precluding dose-response analysis.

The Agency agrees that this study should not be used as the sole determination of mutagenicity, but the lack of traditional controls does not justify excluding this study from consideration because sufficient variation does exist between the results of successive weeks of pairing to indicate dominant-lethal damage to certain stages of the germ cell maturation cycle. This is particularly true in Experiment 1, which most closely follows standard protocols. The post-implantation losses for the early stages of sperm maturation were very similar to the control values, while the spermatids and epididymal sperm were affected sufficiently to produce losses as much as five-fold greater than controls.

(ii) Route of Administration

American Cyanamid Co. (30000/16:#5A), Montedison USA, Inc. (30000/16:#25A), and Menzer (30000/16:#35) indicated that the intraperitoneal route of administration is inappropriate for this type of study.

The Agency has rejected this rebuttal attempt. Intraperitoneal injection of test material is an accepted route of administration in the dominant lethal test. The route of administration was chosen to reduce the variables involved in transporting dimethoate to germ cells. It would be preferable for regulatory purposes, however, to have information derived from the oral route.

(iii) Source of Test Compound

American Cyanamid Co. (30000/16:#5A), Montedison USA, Inc. (30000/16:#25A), and Menzer (30000/16:#35) stated that the dimethoate used in the study was not analyzed by the author and that a definitive source of the material was not given.

The Agency has rejected this rebuttal attempt. Gerstengarbe used the same source for dimethoate as did Gibel et al. (1973) [Letter 1977; Letter 1975]. The dimethoate was obtained from the Bitterfeld Co. and was reported to be 98 to 99% pure. [See Section II.A.(1)(a)(i).]

(iv) Incorrect Dosage Data

American Cyanamid Co. (30000/16:#5A) indicated there may have been a discrepancy in the reported dosages used. The animals may have been given 1/4 the LD_{50} rather than approximately 1/7 of the LD_{50}.

The Agency has rejected this rebuttal attempt. It may be true that the dose was improperly reported, but this would not negate the positive mutagenic effects observed.

(v) Number of Animals Used

American Cyanamid Co. (30000/16:#5A) stated that the numbers of animals reported in the tables in Gerstengarbe (1975) differ from the numbers as stated in the methods section; the discrepancy casts doubt on the statistical analysis.

The Agency has rejected this rebuttal attempt. The lower number of females listed in Gerstengarbe's discussion (see table on page 13 of that study) referred only to those females with a plug. There is a discrepancy in the numbers of males in Experiment 1 (40 males were listed in the discussion, p.13, and 36 in the methods section p.8). Gerstengarbe (Letter 1977) indicated that the correct numbers are those listed in the methods section on page 8 of the translation. The increase in both post- and pre-implantation losses over the control group (5- and 3-fold increases, respectively) are large enough to suggest a positive result, despite any uncertainty about the statistical analysis.

(vi) Dose/Sperm Relationship

The California Department of Food and Agriculture (30000/16:#36) argued that the relationship between the dose, sperm maturation, storage, and ejaculation is not clear. An animal administered 80 mg/kg of dimethoate would probably be unable to copulate for several hours afterward.

The Agency has rejected this rebuttal attempt. The animals were treated only once, one day before pairing in Experiments 1 and 2, which were the most important tests. The rebuttal statement, therefore, applies only to the long-term test (Experiment 4). The inability to copulate would merely serve to reduce the percentage of females observed with plugs; however, there were sufficient females remaining to complete the study.

(i) Bhunya and Behera (1975)

(i) Lack of Control Data

American Cyanamid Co. (30000/16:#5A) indicated that no control data were given in this study.

The Agency has rejected this rebuttal attempt. The authors stated that control animals were used, but no data were listed in the brief paper (which was in the form of a letter to the editor). The authors indicated, however, that there was a dose-effect relationship between the two doses, which was most pronounced at 48 hours (17% of cells with aberations at the centromere at a dose of 0.5% dimethoate compared with 44% at 1.0% dimethoate). This is sufficient in the absence of specific control data to indicate a chromosome aberration effect at the centromere under the conditions of this study.

(ii) Reversible Effects

American Cyanamid Co. (30000/16:#5A) stated that the effects were reversible after 72 hours, and that it is doubtful if they could be heritable.

The Agency has concluded that this rebuttal is partially successful. There is a great reduction in the number of aberrations with time, but at 72 hours there is still a slight dose-response effect (11% aberrations for 0.5% dimethoate and 15% for 1.0% dimethoate). The reduction may be due to a cytotoxic effect. The question of heritability is not resolved by this study.

(j) New Studies Offered in Rebuttal

(i) American Cyanamid Co. (1977)

American Cyanamid Co. (30000/16:#5A) performed a bacterial assay using *E. coli* WP-2 $UvrA^-$ and found that "Dimethoate was not mutagenic" even at "extremely high doses."

The Agency has rejected this rebuttal attempt. The registrant repeated the spot test using the method and strain used by Hanna and Dyer (1975); the test was again positive (this result was not mentioned in the rebuttal). Dimethoate exhibited an excellent dose-response curve from 100 ug/plate (11 revertants/plate) to 10,000 ug/plate (265 revertants/plate), which shows that dimethoate does indeed induce mutagenic activity. Based on their study, the registrant stated that dimethoate is a non-mutagen because of its "potency" of less than 0.01 revertants/nanomole. The statement that dimethoate is a non-mutagen is not correct by this criterion because: 1) *E. coli* WP2 was not the organism used by the Ames group which originated this particular definition of potency; and 2) the criterion for determining a cut-off point for mutagenicity has not been firmly established (Ashby and Styles 1978a; Ashby and Styles 1978b; Ames and Hooper 1978; McGregor 1978).

(ii) Ashwood-Smith et al. (1972)

American Cyanamid Co. (30000/16:#5A) cited a study by Ashwood-Smith et al. (1972) which found dimethoate to be non-mutagenic in *E. coli* UvrA.

The Agency has rejected this rebuttal attempt. Ashwood-Smith et al. stated only that they used E. coli WP2 (try-), not the specific cryptic mutation UvrA (which is unable to excise thymine dimers). Their results, therefore, are in agreement with Hanna and Dyer (1975) who also found E. coli WP2 to show negative results in a spot test. Even if Ashwood-Smith et al. had used E. coli WP2 UvrA, they used only 1,000 ug/disc, which is less than the amount American Cyanamid Co. (1977) found necessary for positive results.

(4) Other Comments

In addition to the risk criteria discussed above, the RPAR notice listed two other possible adverse effects of dimethoate for which insufficient evidence existed to initiate a rebuttable presumption. The Agency requested registrants and other interested parties to submit data on delayed neurotoxicity and synergism of dimethoate by other pesticides. The Agency has received comments concerning these effects and concludes that there is insufficient evidence upon which to base a regulatory decision.

(a) Delayed Neurotoxicity

American Cyanamid Co. (1965b) performed demyelination studies for dimethoate and its oxygen analog, dimethoxon, in white leghorn hens. Because the data from this study were inconclusive, the Agency requested comment on dimethoate's ability to induce delayed neurotoxicity.

American Cyanamid Co. (30000/16:#5A) indicated that the Bitterfeld study discussed in Section II.A.(b) demonstrated that dimethoate does not produce delayed neurologic pathologies.

The Agency rejects the Bitterfeld study as evidence that dimethoate does not induce delayed neurotoxicity. Since only macroscopic analyses were performed in this study, there is no expectation that neurotoxicological pathologies would have been detected.

The Agency concludes that insufficient evidence exists to determine whether dimethoate can induce delayed neurotoxicity and that the submission of new evidence concerning dimethoate's ability to induce delayed neurotoxicity is warranted.

(b) Synergism of Dimethoate by Other Pesticides

Uchida et al. (1966) have reported on synergism of dimethoate by EPN in mammals and insects. (Synergism is defined as the greater toxicity of two compounds together than would be anticipated from the sum of their individual effects.)

American Cyanamid Co. (30000/16:#5A) pointed out that dimethoate and EPN are generally not mixed and used together. The Agency concludes that there is insufficient evidence to indicate that dimethoate exceeds the risk criteria enumerated in 40 CFR 162.11 based on its possible synergism by other compounds.

B. Exposure Analysis

The Agency has revised and expanded the exposure analysis discussed in Position Document 1. This revised analysis considers rebuttal comments received in response to the RPAR notice, data from USDA concerning use and use practices, and published studies concerning worker exposure to dimethoate and related pesticides.

In agriculture dimethoate is applied aerially or by ground rig. Around the home, dimethoate is usually applied by a hand-held sprayer. This exposure analysis will assess applicator exposure under both the aerial and ground application situations, as well as general population exposure (i.e., through food residues).

(1) Exposure Due to Aerial Application

There are no published data available showing the amount of dimethoate an applicator will be exposed to during aerial application. Exposure data is available, however, for another organophosphate, parathion. Because the Agency is concerned with teratogenic effects, exposure values will be calculated based on a 60 kg female. Therefore, the exposure values reported for parathion during aerial application (Gordon et al. 1978) are used as a model for estimating human exposure to dimethoate during aerial application. This analysis will evaluate exposure to pilots and associated ground crews supporting the aerial application activity. The rationale for using parathion values to estimate dimethoate exposure is as follows:

1) The vapor pressures of parathion (0.942×10^{-5} mm Hg at $25^{\circ}C$) and dimethoate (2.5×10^{-5} mm Hg at $25^{\circ}C$) are comparable. It is generally recognized that the residues of pesticides with relatively low volatility in the air during or immediately after application are predominantly present in the form of droplets and particles;

2) The formulation most often used for both parathion and dimethoate is an emulsifiable concentrate (E.C.); and

3) The rates of aerial application of parathion (0.25 to 2.0 pounds a.i./2 gallons of water) and of dimethoate (0.5 to 1.5 pounds a.i./2 gallons of water) are similar.

Exposure during aerial application can occur via the respiratory or dermal route.

(a) Respiratory Exposure

In calculating inhalation exposure, the following assumptions are made:

1) the ambient air concentrations observed for parathion (Gordon et al. 1978) are the same as dimethoate at each of the various sampling sites (e.g., airplane cockpits);

2) the applicator's breathing rate will be 1.8 m^3 per hr;

3) 100% of all dimethoate inhaled will be absorbed;

4) the applicator will weigh 60 kg (adult female); and

5) the applicator will wear no special protective devices (e.g., respirator).

The following equation (memo 1979b) is used in calculating the respiratory exposure for dimethoate:

$$\begin{array}{c}\text{Respiratory}\\ \text{Exposure}\\ \text{(ug/kg/day)}\end{array} = \frac{\begin{array}{c}\text{ambient air concentration of}\\ \text{dimethoate (ug/m}^3\text{) at the}\\ \text{site in question}\end{array} \times \begin{array}{c}1.8\ \text{m}^3\text{/hr}\\ \text{(breathing}\\ \text{rate)}\end{array} \times \begin{array}{c}\text{number of hours of}\\ \text{exposure/day}\end{array}}{\text{60 kg person}}$$

Data concerning the number of hours of exposure for each activity (e.g., pilot spraying corn) was obtained by the USDA/EPA Dimethoate Benefit Assessment Team (USDA/EPA Assessment Team on Dimethoate, 1979).

(b) Dermal Exposure

In calculating dermal exposure the following assumptions are made:

1) dermal exposures observed for parathion skin patch tests (Gordon et al. 1978) are the same for dimethoate;

2) 15% of the applicator's total skin surface will be exposed;

3) 10% of the dimethoate coming into contact with the uncovered skin will be absorbed; and

4) the applicator will weigh 60 kg (adult female).

The following equation (memo 1979b) is used in calculating the dermal exposure to dimethoate.

$$\text{Dermal Exposure (mg/kg/day)} = \frac{\text{concentration of dimethoate on the skin (ug/cm}^2\text{)} \times 3000\ \text{cm}^2 \times 10\ \%\ \text{absorbed} \times \text{number of hours exposed per day}}{60\ \text{kg person}}$$

(2) Exposure Due to Ground Application: Respiratory and Dermal Exposure

(i) Boom and Compressed Air Application Situations

Dimethoate is often applied using boom type equipment in large agricultural situations and by compressed air equipment (hand pump sprayers) in home garden application situations. Specific data concerning applicator exposure to dimethoate under these conditions in the U.S. is not available. However, similar information concerning applicator exposure to dimethoate in the Sudan is available.

In the Sudan, a survey was carried out on the exposure of spraymen applying dimethoate. The final spray concentration was 1.27 g/liter (Copplestone et al. 1976). All of the spraymen used a knapsack mist blower which was powered by a two-stroke engine and had a liquid capacity of 10 liters. A 2-mm diameter nozzle was used. One liter of solution was delivered each minute at a constant pressure of 152KPa (22 psi). Therefore, the tank was refilled about every 10 minutes. The dermal and respiratory exposure of spraymen to dimethoate, which was reported in that study, is used as the basis for all the exposure analysis calculations of dimethoate during boom and compressed air equipment application in this analysis.

It should be noted, however, that using the exposure figures developed by Copplestone et al. (1976) will probably result in an overestimation of boom rig type applicator exposure in the U.S. In the Sudan the applicators carried the sprayer on their backs which dispensed the spray solution under pressure in a wide mist pattern. The applicators, therefore, walked forward into their own spray. In the U.S. dimethoate is applied by mechanical sprayers which are equipped with wheels and are pulled behind by tractors. The applicator drives the tractor and is well forward of the spray. Because the applicator (tractor driver) is generally forward of the spray, actual exposure would be less than that experienced by applicators in the Sudan. However, because the Agency is not aware of studies showing applicator exposure during application of dimethoate in the U.S., the data obtained in the Sudan (Copplestone et al. 1976) will be used for this analysis. Applicator exposure resulting from the use of compressed air type equipment (e.g. hand held sprayers used around the home) would be expected to closely approximate the Sudan exposure data.

The following equations (memo 1979b) are used to calculate the respiratory and dermal exposure resulting from the ground application of dimethoate.

$$\text{Respiratory Exposure} = \frac{\text{respiratory exposure observed in Sudan (mg/hr)} \times \dfrac{\text{concentration of dimethoate used in the U.S.}}{\text{concentration of dimethoate used in the Sudan}} \times \text{number of hours spraying (USDA/State/EPA Assessment Team on Dimethoate).}}{\text{60 kg person}}$$

$$\text{Dermal Exposure} = \frac{\text{dermal exposure observed in the Sudan (mg/cm/hr}^{2}\text{)} \times \dfrac{\text{concentration of dimethoate used in the U.S.}}{\text{concentration of dimethoate used in the Sudan}} \times \text{10\% absorption}}{\text{60 kg person}}$$

Dimethoate is registered for use on a wide variety of agricultural commodities. Time, however, precluded an in-depth exposure analysis of every use. The USDA/EPA Benefit Assessment Team on Dimethoate (1979) identified those uses which account for the majority of the dimethoate used, as well as uses which do not represent high annual use but are important minor uses. These uses and the estimated combined dermal and inhalation exposure are found in Table II.

(ii) Air Blast Application Situations

High volume air blast application equipment (greater than 300 gal./A) is commonly used in citrus, pecans and pome fruit (apples and pears) orchards. Specific data concerning applicator exposure to dimethoate under these conditions is not available. Wolfe et al. (1967), however, reported the dermal and respiratory exposure of workers to several selected pesticides using airblast equipment. In the absence of specific dimethoate data the Agency will assume the exposure values of workers applying 0.05% parathion E.C. to be the same as dimethoate. The Agency feels this assumption is reasonable because both dimethoate and parathion are organophosphates and both are emulsifiable concentrates applied at similar concentrations.

Air blast equipment is also used when treating grapes. In the case of grapes, however, dimethoate is applied in a low volume air carrier/semi-concentrate form (approximately 40-50 gal/A.). Because the spray concentration for grapes is higher than that of citrus, pecans and pome fruits the Agency will use the Copplestone model (Copplestone et al., 1976) when calculating worker exposure during application of dimethoate to grapes.

(3) Exposure to Farm Workers

Exposure to dimethoate can also occur when farm workers enter treated fields to cultivate or otherwise manage the treated field. Exposure to this subgroup, however, is expected to be very low. It has been shown

(Nelson, et al. 1966, Menzer and Thomas 1970) that dimethoate residues degrade rapidly after spraying. It is unlikely, in the light of modern cultural practices and the established preharvest interval of up to 28 days after treatment, that workers would enter fields immediately after treatment. Workers entering treated fields several days after treatment are not expected to encounter high exposure due to residues on treated crops. In addition, dimethoate is somewhat systemic in nature in that it passes through the surface of the plant and is translocated within the plant, thereby further reducing the possibility of worker exposure.

(4) General Population Exposure

The general population exposure to dimethoate and concurrent risk resulting from eating treated foods is discussed in Section II.C.(3)(b)(i) and presented in Table II. Little information is available on dimethoate residues on crops at harvest; therefore, the Agency assumes these residues to be present at tolerance level (memo 1979c). Not all crops for which dimethoate is registered are actually treated with dimethoate. The percent of each crop treated, therefore, was included in the calculation of oral exposure (memo 1979c).

C. Risk Analysis

Three risk criteria were identified for dimethoate in Position Document 1: oncogenicity, mutagenicity, and reproductive and fetotoxic effects. The Agency has reviewed comments submitted in response to these risk criteria and has utilized these comments in formulating risk assessments for each of these risk criteria.

Table II

Calculated Combined Dermal, Inhalation, and Oral Exposure Values During Aerial and Ground Applications of Dimethoate to Various Crops

CROP	TYPE OF SPRAYING	SUBGROUP	Combined Dermal and Inhalation DAILY EXPOSURE (mg/kg/day)	ORAL EXPOSURE (mg/kg/day)	TOTAL EXPOSURE (mg/kg/day)
corn	air	pilots	0.0083	0.0032	0.012
corn	air	flaggers	0.008	0.0032	0.011
corn	air	mixer/loader	0.0063	0.0032	0.010
ornamental	ground	commerical high concentration compressed air	0.00012	0.032	0.0033
ornamental	ground	home garden high concentration	0.000152	0.0032	0.00335
grape	ground	Boom highest conc.	0.0012	0.0032	0.0044
grape	ground	Air carrier (custom) Coppelstone *et al*.	0.0207	0.0032	0.0239
grape	ground	dust	0.130	0.0032	0.1332
cotton	air	pilot	0.0017	0.0032	0.005
cotton	air	mixer/loader	0.00095	0.0032	0.00042
cotton	ground	applicators	0.0078	0.0032	0.0011
cotton	ground	mixer/loader	0.00033	0.0032	0.004
citrus	air	pilot, ground crew mixer/loader	same as corn		

Table II (continued)

CROP	TYPE OF SPRAYING	SUBGROUP	Combined Dermal and Inhalation DAILY EXPOSURE (mg/kg/day)	ORAL EXPOSURE (mg/kg/day)	TOTAL EXPOSURE (mg/kg/day)
citrus	ground (airblast)	applicators mixer/loader	0.39	0.0032	0.3932
sorghum	air	same as corn			
veg. field (tomato, broccoli)	air	pilot	0.013	0.0032	0.0162
		flaggers	0.013	0.0032	0.0162
		mixer/loader	0.0062	0.0032	0.0094
veg. (Fla)	ground	applicator	0.00005	0.0032	0.0033
vector control (house fly)	ground	applicator	0.0019	0.0032	0.0051
forest pine (seed orchard)	ground	applicator	0.0008	0.0032	0.0040
pecan	ground (airblast)	applicator mixer/loader	0.119	0.0032	0.12
safflower	air	same as corn			
pome	ground (airblast)	commercial applicator including mixer/ loader	0.242	0.0032	0.245
pome	ground	hose sprayer	0.00017	0.0032	0.0034

Table II (Continued)

CROP	TYPE OF SPRAYING	SUBGROUP	Combined Dermal and Inhalation DAILY EXPOSURE (mg/kg/day)	ORAL EXPOSURE (mg/kg/day)	TOTAL EXPOSURE (mg/kg/day)
soybean	air	same as corn			
wheat	air	same as corn			
tobacco High conc.	ground	applicator including mixer/ loader	0.00042	0.0032	0.0036
alfalfa High conc.	ground	applicator including mixer/ loader	0.00052	0.0032	0.0084
veg. fields (lettuce)	ground	applicator	0.0002	0.0032	0.0034
		mixer/loader	0.00026	0.0032	0.0035

(1) Oncogenicity Risk Analysis

The Agency has reviewed rebuttal comments submitted in response to the oncogenicity risk criteria discussed in the RPAR notice and accompanying position document. In Section II A.(1), the Agency responded to rebuttal comments and concluded that the individual rebuttal comments do not invalidate the oncogenic risk criterion. However, based on a re-analysis of the studies involved and the rebuttal comments as a whole, the EPA Carcinogen Assessment Group has concluded that the weight of evidence for carcinogenicity of dimethoate is only suggestive, warranting further studies, but not adequate to justify a quantitative assessment of cancer risk.

There were two studies involved: Gibel et al. (1973) and NCI (1977). The Gibel study, showing positive results in rats, was poorly documented and very weakly positive. There was an excess cancer occurrence only when the total yield of tumors of all types and of both sexes were combined. The NCI study in rats and mice was negative, but this study was one of the early NCI bioassays which used only 10 matched control animals. Furthermore, the NCI study cannot be directly compared with the Gibel study. Gibel used a different strain of rat and although there was severe toxicity of the blood-forming tissues in the Gibel study, no such effect was observed in the NCI study.

In more detail the results of the two studies were as follows:

Gibel et al. (1973) reported the effect of dimethoate on 10-week old Wistar rats of both sexes. The compound was given by gavage twice weekly at 5, 15, and 30 mg/kg dose levels. One group of animals was also given 15 mg/kg intramuscularly. Treated animals showed strong hyperplasia of blood-forming parenchyma of the bone marrow involving erythropoesis, granulopoesis and megakaryopoesis. Non-bony myeloid metaplasia, primarily in the liver and spleen, was seen in 59% of treated animals. In addition granulyocytosis was found in 22% of the animals. There was a significant increase in malignant tumors when all sites were combined among treated animals at the highest dose levels for both oral and intramuscular routes of administration. No significant difference was found in benign tumors, but when benign and malignant tumors were combined, the incidence was statistically significant in the high dose group. The Agency considers a chemical to be a presumptive cancer risk when it causes a statistically significant excess incidence of benign or malignant tumors in humans or animals (Albert et al., 1977).

The authors also studied the effect of dimethoate applied percutaneously twice a week for six weeks to mice of AB strain. The concentration of dimethoate was not stated. The spleen showed considerable metaplasia, frequently with complete atrophy of white pulp. The red pulp showed a partially localized and diffuse myeloid proliferation with numerous immature cell forms, which made it difficult to recognize the basic structure. The authors felt that the mice also developed a myeloproliferation syndrome similar to that observed in Wistar rats.

In 1977, the National Cancer Institute bioassay program completed a feeding study in Osborne-Mendel rats and B6C3F1 hybrid mice of both sexes. The time-weighted average doses were 310 and 155 ppm for male rats, 384 and 192 ppm for female rats and 500 and 250 ppm for mice of both sexes. Pathologic evaluation revealed no statistically significant increase in tumors associated with dimethoate treatment in either species of animal, and it was concluded that there was no carcinogenic effect under the conditions of the experiment. No significant changes were noticed in the hematopoietic system in rats or mice in the NCI study.

In summary, the evidence for carcinogenicity is only suggestive. Therefore, the Agency concludes that a dimethoate oncogenicity study with the same strains of mice (AB mice) and rats (Wistar) used by Gibel is warranted.

(2) Mutagenicity Risk Analysis

One of the risk criteria for which the Agency issued an RPAR against dimethoate was mutagenicity. After reviewing the comments and rebuttals on this presumption of risk, the Agency concluded that the risk had not been rebutted. This section presents an analysis of mutagenicity studies on dimethoate and attempts to draw conclusions relative to human risk from dimethoate's ability to induce mutagenic effects and concludes that risk is very low.

(a) Relevant Positive Tests

(i) Reverse Mutation Bacterial Assays

Dimethoate has been shown to be mutagenic in a reverse mutation spot assay using two strains of *Escherichia coli*, *E. coli* WP 67 (Hanna and Dyer 1975) and *E. coli* WP 2 uvrA (Hanna and Dyer 1975; and American Cyanamid 1977). Mutagenicity was also demonstrated in a quantitative reverse mutation plate assay using *E. coli* WP2 uvrA and *Salmonella typhimurium* TA100 (American Cyanamid 1977). Many other strains of bacteria were tested with negative results. The relative mutagenic potency of a chemical cannot be determined with a spot test; however, a low potency for dimethoate was suggested in the spot tests by the necessity to incubate the plates 72 hours rather than 48 hours to see any positive results with *E. coli*.

A low mutagenic potency for dimethoate was confirmed with *E. coli* WP2uvrA in quantitative plate assays. The positive control, N-methyl N'nitro-nitrosoguanidine (MNNG), at 20 ug/plate produced greater than 1,000 revertants/plate while 10,000 ug/plate of dimethoate produced an average of 310 revertants/plate (American Cyanamid 1977). Thus dimethoate is at least 1,600 times less potent than MNNG under the conditions of this assay. The results with *S. typhimurium* TA100 displayed a similar relationship but were difficult to quantify since a decrease in the dose response curve was seen at 1,000 ug dimethoate/plate and the cells were killed at 10,000 ug/plate. In the TA-100 S9 activated system the highest number of revertant colonies observed was 594 at 1,000 ug/plate dimethoate (although this figure was undoubtedly reduced by the toxicity); MNNG, at 20 ug/plate, produced > 3,000 revertants/plate. The unactivated TA100 assay suggested mutagenicity but it is not reliable since the negative controls had an extremely high background count (522 revertants/plate).

(ii) Forward Mutation Bacterial Assay

Dimethoate was shown to induce forward mutations in *E. coli* K-12 as detected by resistance to 5-methyltryptophan (Mohn 1973). The potency, however, is relatively low compared to the positive controls, MNNG and methyl methanesulfonate (MMS) [Mohn 1973]. 1×10^{-3}M dimethoate was required to produce a mutation frequency similar to that produced by only 1.7×10^{-7}M MNNG; thus dimethoate is about 2,000 times less potent than MNNG under the conditions of this assay.

(iii) Dominant-Lethal Assay (Mouse)

Dimethoate was shown to significantly increase resorptions after treatment of the male AB Jena-Halle mice during the first through the fifth week of sampling. The usefulness of this data for a is limited since a non-standard protocol (which included the intraperitoneal injection of test material and the omission of positive controls) was employed in the study.

(iv) Yeast Gene Conversion Assay

Mitotic gene conversion was induced by dimethoate in *Saccharomyces cerevisiae* D4 (Fahrig 1973). The potency of dimethoate is low; 50 mM dimethoate induced about the same number of conversions as 0.5 mM of the MMS control.

(v) Unscheduled DNA Synthesis in Mammalian Cells

Ahmed et al. (1977) reported an increase in unscheduled DNA synthesis in SV-40 transformed human cells (VA-4) after administration of 100 uM and 1000 uM dimethoate with metabolic activation. Results were negative ($p < 0.5$) at 100 uM and 1000 uM without metabolic activation. No significant ($p < 0.05$) increase was reported after administration of 10 uM with or without metabolic activation.

This study is of limited value for purposes of risk assessment due to a lack of quantification. The authors, for example, used only 3 dose levels and reported results as positive or negative. This precluded determining if there was a dose response relationship. In addition no positive controls were used so the activity of the pesticides studied cannot be related to a known mutagen.

This study does indicate, however, that dimethoate has a potency at least 100 X less than other pesticides that were found to increase unscheduled DNA synthesis in this particular assay. Chlordane, aldrin, dieldrin, carbaryl, diquat, 2,4-D and captan were all reported as positive at the lowest level tested (1 uM) while dimethoate was reported as negative at 10 uM and positive at 100 uM.

(b) Studies Suggestive of Mutagenesis

(i) Plant Cytological Analysis

Amer and Farah (1974) studied the cytology of *Vicia faba* and *Gossypium barbadense* after exposure to dimethoate. A dose-response effect was seen in the percentage of abnormal mitoses, but the effects were probably due to spindle disturbances. Some fragmentation and bridge formation were seen but were not dose-related. The study provides limited information on mutagenic effects and, at best, is suggestive of mutagenesis in *V. faba*.

Amer and Farah (1976) conducted further studies on the effect of dimethoate on the cytology of *V. faba*. In meiosis, spindle "disturbances" were the primary effect. Stickiness and sticky bridges were also reported, but these effects can be caused by other chemicals considered not to be mutagenic (Kihlman 1971). A low percentage of fragmentation was reported. It was not possible to determine the background levels for this effect since the distribution of effects in negative controls was not described. The authors also found that the transmission of these effects to following generations was very low.

Agarwal et al. (1973) studied the effect of dimethoate on the bean, *Phaseolus vulgaris*. The study was inadequately reported. No negative or positive controls were used for the chromosome scoring experiment. Fragmentation was not dose-related. Stickiness was also reported as a major effect but may not be an indication of mutagenicity. This study is at best only suggestive of mutagenesis and, as mentioned above, of little value in determining mammalian risk.

(ii) Mammalian Cytogenetic Analysis

Bhunya and Behera (1975) studied the effect of dimethoate on bone marrow cell chromosomes of adult mice, *Mus musculus*. Although the paper reported that a substantial number of chromosome breakage effects at the centromere are caused by dimethoate the experiment is inadequately reported and is in abstract form. The authors for example, stated that controls were performed but none were presented in the abstract. Since no supporting data is available, this abstract should not be used as a primary determinant for risk analysis and regulation.

(c) Negative Tests

Ashwood-Smith et al. (1972) reported that dimethoate was negative for mutagenic effects in a reverse mutation spot test assay using E. coli WP2 try $^{-}$. This result is in agreement with Hanna and Dyer (1975) and Shirasu et al. (1976).

Shirasu et al. (1976) reported that dimethoate was negative for mutagenic effects in a recombination deficient assay using *Bacillus subtilis* H 17 Rec^{+} and *B. subtilis* M45 Rec^{-}. They also reported negative results in a reverse mutation assay using *E. coli* WP2 B/r try^{-}. *E. coli* WP2 try^{-}hcr is the same strain used by Hanna and Dyer (1975) and American Cyanamid (1977) (they used the notation WP2 uvrA^{-}) in studies which showed positive results after incubation of the plates for 3 days. Shirasu et al., however, incubated their plates for two days; the negative results were clearly due to their insufficient incubation time.

Table III
Summary of Dimethoate Mutagenicity Studies

Paper	Study	Results	Comments
		Haploid Microorganisms	
Hanna & Dyer (1975)	Salmonella typhimurium		
	his C117	-	These test were spot tests using "a crystal or 5-10 ul of each chemical" directly onto the bacterial lawn
	his G46	-	
	his D3053	-	
	TA 1530	-	
	TA 1531	-	
	TA 1532	-	
	TA 1534	-	
	TA 1535	-	
	Escherichia coli		
	WP2	-	
	WP2 uvrA	+	Revertants were not seen until after 72 hr incubation (try-, uvrA-)
	CM561	-	
	CM571	-	
	CM611	-	
	WP67	+	Required 72 hr. incubation. (try$^-$, urvA$^-$, polA$^-$)
	WP12	-	
American Cyanamid Co. (2/2/77)	Salmonella typhimurium		plate tests, with and without S 9
	TA 1530	-	200 ug/plate
	TA 1535	-	1,000 ug/ plate
	TA 100	-	1,000 ug/plate
	TA 1538	-	200 ug/plate
	TA 98	-	1,000 ug/plate
	TA 1537	-	1,000 ug/plate
	E. coli WP2 uvrA	-	1,000 ug/plate, 48 hour incubation

Table III (continued)

American Cyanamid	*S. typhimurium* TA 1535	-	disc tests, 1,000 ug/plate, 72 hrs incubation (11/16/77)
	TA 98	-	10,000 ug/plate
	TA 100	-	10,000 ug/plate
	TA 1537	-	10,000 ug/plate
American Cynamid (11/16/77)	*E. coli* WP-2 uvrA$^-$	+	disc tests at 10,000 ug/plate dimethoate
	S. typhimurium TA 1535	-	plate tests, 10,000; 1,000; 100; and 0,48 hours incubation
	TA 1537	-	
	TA 98	-	
	TA 100	+	high spontaneous mutation rate, toxic response at 10,000 ug/plate
	TA 1538	-	
	E. coli WP-2 uvrA$^-$	+	10,000, 5,000, 1000, 100, 0 ug/plate, good dose response curve, no difference with or without S-9, MNNG (no dose given) produced 71,000 revertants/plate while dimethoate produced 254 to 456 revertants/plate at 10,000 ug/plate
Mohn (1973)	*E. coli* K12 forward mutation to 5-MT resistance	+	much less potent than controls, 1.7 x 10^{-7}M - MNNG concentration approx. equivalent to 1.0 x 10^{-3}M - dimethoate concentration

Table III (continued)

Shirasu et al. (1976)	*Bacillus subtilis* H17 Rec$^+$ assay	-	spot test: inoculum of dimethoate onto disc was 0.2 ml of 1 mg/ml solution
	B. subtilis M45 Rec$^-$ assay	-	"
	E. coli WP2 B/r try$^-$ reversion assay	-	"
	E. coli WP2 try "hcr" uvrA) reversion assay	-	"
	S. typhimurium TA 1535 reversion assay	-	"
	" TA 1536	-	"
	" TA 1537	-	"
	" TA 1538	-	"
Ashwood-Smith et al. (1972)	*E. coli* WP2 try$^-$ reversion assay	-	spot test, 1 ug/disc.
Gerstengarbe 1975	Mouse-dominant-lethal	+	i.p. route of inoculation, no positive controls, non-standard protocols used.
Fahrig (1973)	*Saccharomyces cerevisiae* D4 gene conversion	+	0.5 mM MMS control induced approx. same number of convertants as 50 mM Dimethoate
Agarwal et al. (1973)	Cytology of *Phaseolus vulgaris*	(+)	no controls, no dose-response at metaphase
Amer and Farah (1974)	Cytology of *Vicia faba*	(+)	no controls reported, "non-transmissable" spindle effects were the primary aberration reported
Amer and Farah	Cytology of *Vicia faba* and *Gossypium barbadense*	(-)	no controls reported, primarily spindle effects were reported
Bhunya, et al. (1975)	Cytogenetic mouse study	+	poorly reported, questionable validity
Ahmed, et al.	Unscheduled DNA synthesis in transformed mammalian cells	+	no positive controls were reported, effects were not numerically quantified

(d) Summary

Dimethoate has been shown to be mutagenic in bacteria, in transformed mammalian cells, and with less certainty in a strain of mouse (dominant lethal assay). There are three studies which strongly suggest mitotic disturbances in plants and one study, poorly documented, which suggests chromosome abnormalities in mice. These studies are summarized in Table III.

The data available to the Agency indicates that dimethoate: 1) causes gene mutations in bacteria but not in eukaryotic systems, 2) is suspected of producing spindle effects which predispose to numerical chromosome aberrations (data in higher plants only), 3) causes dominant lethal effects in mammals (study used nonconventional protocol), 4) causes chromosome breakage in mammalian bone marrow. Thus there is some evidence that dimethoate can produce chromosome aberrations in mammalina systems. In addition, the dominant lethal study indicates the potential for the chemical to reach the target gonad cells. The chromosomal effects produced by dimethoate in higher systems plus the ancillary information in eukaryotic microorganisms showing gene conversion, coupled with the evidence suggesting that the chemical reaches the mammalian gonad, leads the Agency to conclude that humans may be a risk from exposure to dimethoate. Additional studies are required to substantiate this mutagenic risk, and to estimate the magnitude of the risk.

There appears to be some qualitative evidence bearing on the mutgenic potential of dimethoate. The only studies which can be used for a quantitation of potency are the bacterial assays and the yeast gene conversion assay. These, however, show a very low order of potency, near lower detection limits, and were noted in only a few of the many strains used. The mammalian cell unscheduled DNA synthesis assay, although not suitable for numerical quantification, also indicates a low potency compared to other pesticides studied.

It is generally agreed by the scientific community that a risk assessment for human hazard connot be made from microbial data alone since these studies are performed in repair deficient cells and are unassociated with normal mammalian metabolic processes. The dominant-lethal assay does show that mutagenic events may occur in mice at relatively high i.p. doses of dimethoate. The metabolism studies, however, show a rapid elimination of dimethoate and its metabolites from the body with minimal amounts remaining in germinal tissues.

The Agency concludes that dimethoate has a relatively low mutagenic potency which is shown by submammalian assays and by the metabolic studies. This low potency, together with low exposure as discussed in Section B, indicates that human risk is low. Additional test data is necessary to evaluate the quantitative risk of this compound. The Agency's Mutagenicity Guidelines will indicate suitable assays.

In light of the available evidence which indicates that Dimethoate may pose a potential mutagenic risk to humans, the Agency believes it is prudent to take appropriate measures to reduce the potential mutagenic hazard as discussed in Section IV C.

(3) Reproductive and Fetotoxic Effects Risk Analysis

(a) New Data

New data (Khera unpublished) showing a dimethoate formulation to be a mild teratogenic agent has been received by the Agency. There data were unavailable at the time the RPAR was issued.

Khera (unpublished) administered Cygon 4E containing 47.3% dimethoate to pregnant cats (in gelatin capsules) on days 14 to 22 of gestation. The doses were 0, 3, 6, or 12 mg/kg per day of Cygon 4E which corresponds to 0, 1.4, 2.8, or 5.7 mg/kg per day of dimethoate. On day 43 of gestation, the fetuses were removed, weighed, and examined.

There were no signs of maternal toxicity in any cats treated. Dimethoate, at all doses tested, caused no effect on the number of live fetuses, resorption, dead fetuses, or mean fetal weight. Both the total number of anomalous fetuses and the number of litters having anomalous fetuses were increased at the high dose when compared to controls, but this increase was not statistically significant (p=0.05, Student + Test). When the incidence of one abnormality (polydactyly, or increase in the number of digits on the paws) at the high dose was compared to the controls, the results were statistically significant.

There was no dose-response noted at 3 or 6 mg/kg with regard to any anomaly, including polydactyly. Although a no-adverse effect level for all parameters can be set at 6 mg/kg per day of Cygon 4E, the author (Khera) indicated that this teratogenic effect should be verified through additional testing. This additional testing would determine if the effect were due to dimethoate itself, the pesticidally inert ingredients, or the combination of these (Cygon 4E).

The same dimethoate formulation, Cygon 4E, was tested at doses of 0, 3, 6, 12, or 24 mg/kg per day (corresponding to 0, 1.4, 2.8, 5.7, or 11.3 mg/kg per day dimethoate) in pregnant Wistar rats by oral intubation. There were 20 female rats started in each group, and the number of pregnant dams was 17, 17, 15, 16, and 16, respectively. One dam at the highest dose died from Cygon-induced cholinergic signs of toxicity, and another seven showed similar signs of toxicity but recovered. Decreased maternal weight gain was seen at the high dose, but no adverse maternal effects were noted at the lower doses.

There were no effects of treatment on the number of live fetuses per dam, number of dead or resorbed fetuses, or fetal weight. At doses of 12 and 24 mg/kg per day Cygon 4E, there were significant increases in number of anomalous fetuses/number of fetuses examined and the number of litters having at least one anomalous fetus/number of litters examined, when compared to controls.

When individual variations were examined, the two high doses had a significant (p=0.05) increase in fetuses with wavy ribs. The author (Khera) characterized these anomalies as being "of minor types and of unknown significance." It should be noted that these effects (wavy ribs), which are often considered indicators that the embryotoxic or fetotoxic dose is approached, occurred at either the maternal toxic dose or one-half of that dose. If the only significant effect observed when animals are dosed up to maternal toxic levels is an increase in wavy ribs, then this increase in wavy ribs is considered of marginal importance (Burnam 1979). Again, as in the cat teratology study, the presence of unknown inert ingredients makes interpretation difficult. The no-observed-effect level for any parameters was 6 mg/kg per day of Cygon 4E.

In both studies by Khera, the no-observed effect level was 6 mg/kg per day for Cygon 4E (2.8 mg/kg per day dimethoate). The occurance of minor teratogenic effects at higher doses indicates that Cygon 4E has the potential to interfere with fetal development. Additional studies are required to fully determine the significance of these findings.

(b) Teratogenic Risk

Reproductive risk is generally expressed in terms of margins of safety. The margin of safety (MOS) is the ratio of estimated exposure of a group of people to the dosage level (exposure) causing no-observable adverse effect (NOEL) in an appropriate animal study. The Agency will use the NOEL of 2.8 mg/kg per day as observed by Khera for calculating margins of safety for dimethoate.

(i) General Population Risk

Teratogenic risk can be calculated for two population groups: 1) The General Population and 2) Applicators. The general population would be at risk due to dimethoate residues in food.

The most conservative (worst case) estimate of general population exposure is to assume dimethoate to be present on foods at tolerance levels. Summation of tolerances for all foods treated with dimethoate multiplied by the food factor (percent contribution of each food to total diet) provides a worst case estimate of 0.0085 mg/kg per day for a 60 kg female on an average diet. Not all crops for which dimethoate is registered are actually treated each year. When the percentage of crops actually treated with dimethoate is factored into this worst case estimate, the probable case value becomes 0.0032 mg/kg per day (memo 1979c). The corresponding margins of safety are as follows for the general population exposed to dimethoate through food residues.

$$\text{Worst Case:} \quad \frac{2.8 \text{ mg/kg/day}}{0.0085 \text{ mg/kg/day}} = \text{MOS of } 329$$

$$\text{Probable Case:} \quad \frac{2.8 \text{ mg/kg/day}}{0.0032 \text{ mg/kg/day}} = \text{MOS of } 875$$

The MOS of 329 is unrealistic in that this figure assumes all crops to be treated with dimethoate and residues to be present at tolerance levels. Moreover, it is likely that the probable case MOS of 875 is in itself a gross overestimate of risk as this MOS was derived assuming dimethoate residues to be present at tolerance levels. It is generally recognized that organophosphate pesticides such as dimethoate degrade rather rapidly and that several weeks may elapse between application and consumption of the treated crop. It is likely, therefore, that the MOS for general population risk is several orders of magnitude higher than 875. A lack of data concerning dimethoate residues at harvest, however, precludes estimates of the actual MOS.

(ii) Applicator Risk

Smaller subpopulations engaged in the application of dimethoate would experience greater exposure and concurrent risk than that identified for the general population.

Table IV

MARGINS OF SAFETY FOR VARIOUS USERS OF DIMETHOATE

CROP	TYPE OF SPRAYING	MOS for SUBGROUP	Combined Dermal and Inhalation DAILY EXPOSURE (for female mg/kg/day)	ORAL EXPOSURE	TOTAL EXPOSURE	MOS For Terato-genic Effects (1)
corn	air	pilots	0.0083	0.0032	0.012	233
corn	air	flaggers	0.008	0.0032	0.011	255
corn	air	mixer/loader	0.0063	0.0032	0.010	280
ornamental	ground	commercial high concentration compressed air	0.00012	0.0032	0.0033	843
ornamental	ground	home garden high concentration	0.000152	0.0032	0.00335	836
grape	ground	Boom highest conc.	0.0012	0.0032	0.0044	636
grape	ground	highest conc. (custom) Copperstone model	0.0207	0.0032	0.0239	117
grape	ground	dust	0.130	0.0032	0.1332	21
cotton	air	pilot	0.0017	0.0032	0.005	560
cotton	air	mixer/loader	0.00095	0.0032	0.0042	667
cotton	ground	applicators	0.0078	0.0032	0.0011	255
cotton	ground	mixer/loader	0.00033	0.0032	0.004	700
citrus	air	pilot ground crew mixer/loader	same as corn			

(1) Based on 2.8 NOEL (Khera unpublished)

Table IV (continued)

MARGINS OF SAFETY FOR VARIOUS USERS OF DIMETHOATE

CROP	TYPE OF SPRAYING	SUBGROUP	Combined Dermal and Inhalation DAILY EXPOSURE (for female mg/kg/day)	ORAL EXPOSURE	TOTAL EXPOSURE	MOS for Teratogenic Effects
citrus	ground (air blast)	applicators mixer/loader	0.39	0.0032	0.3932	7
sorghum	air	same as corn				
veg. fields (Tomato, Broccoli)	air	pilot	0.013	0.0032	0.0162	170
		flaggers	0.013	0.0032	0.0162	170
		mixer/loader	0.0062	0.0032	0.0094	298
veg. (Fla)	ground	applicator	0.00005	0.0032	0.0033	848
vector control (house fly)	ground	applicator	0.0019	0.0032	0.0051	549
forest pine (seed orchard)	ground	applicator	0.0008	0.0032	0.0040	700
pecan High conc.	ground	applicator	0.00044	0.0032	0.0036	778
		mixer/loader	0.00022	0.0032	0.00342	819
pecan	ground (air blast) model	applicator mixer/loader	0.119	0.0032	0.122	23
safflower	air	same as corn				
pome	ground (air blast)	commercial applicator including mixer/loader	0.242	0.0032	0.245	12
pome	ground	hose sprayer	0.00017	0.0032	0.0034	823

Table IV (continued)

MARGINS OF SAFETY FOR VARIOUS USERS OF DIMETHOATE

CROP	TYPE OF SPRAYING	SUBGROUP	Combined Dermal and Inhalation DAILY EXPOSURE (for female mg/kg/day)	ORAL EXPOSURE	TOTAL EXPOSURE	MOS for Teratogenic Effects
soybean	air	same as corn				
wheat	air	same as corn				
tobacco High conc.	ground	applicator including mixer/loader	0.00042	0.0032	0.0036	778
alfalfa High conc.	ground	applicator including mixer/loader	0.0052	0.0032	0.0084	333
veg. fields (lettuce)	ground	applicator mixer/loader	0.0002 0.00026	0.0032 0.0032	0.0034 0.0035	823 800

Estimates of exposure to these subpopulations are identified in Section II.B, and the MOS for each subgroup is presented in table IV. MOS figures for applications also include dietary exposure.

(4) Fish and Wildlife Risk Analysis

The Agency did not presume against dimethoate based on acute toxicity to aquatic, avian, or mammalian species. The Agency has, however, identified those uses of dimethoate which would result in the greatest potential environmental impact. This section presents an analysis of risk to aquatic and terrestrial wildlife from dimethoate use on cotton (aphids, thrips, fleahoppers, and plant bugs), on alfalfa seed crop (lygus bugs), and on citrus (aphids).

Rates and numbers of applications of dimethoate for use on cotton, alfalfa seed crop and citrus are shown below:

Use	Application Rate (lbs a.i./A)*	Number of Applications (per season)
Cotton	0.1 - 0.2	1 - 3
Alfalfa Seed Crop	.5	1
Citrus	1.25 - 2.0	multiple

* Pounds active ingredient/acre.

Environmental fate data indicate dimethoate can be retained in the environment for a period of time sufficient to allow potential exposure to aquatic and terrestrial wildlife species (memo 1978c). The EPA Pesticide Incident Monitoring System (PIMS) shows one suspected runoff-caused fish kill in a stream adjacent to a dimethoate treated field (EPA 1978b).

Acute toxicity values for aquatic species tested ranged from 6.0 ppm to 155 ppm for fish and 0.043 ppm to 0.4 ppm for invertebrates. The lowest acute toxicity values reported were 96-hour LC_{50} concentrations of 6.0 ppm for the bluegill sunfish, Lepomis macrochirus (USDI 1964) and 0.043 ppm for the stonefly, Pteronarcys californica (Sanders and Cope 1968). Five-day LC_{50} concentrations reported for terrestrial wildlife ranged from 332 ppm for pheasants (Phasianus colchicus) to 1011 ppm for mallards (Anas platyrhynchos) [Hill et al. 1975]. A field study conducted to determine the effects of dimethoate applied at 0.25 and 0.50 pounds/acre (clover) on small mammals failed to show direct impacts (Barrett and Darrell 1967). Researchers speculated that a decline in a house mouse (Mus musculus) population was due to a decreased food supply.

At recommended use rates for cotton and alfalfa seed crop, initial residues of dimethoate on terrestrial wildlife food sources in and around treated fields would range from 2.3 to 50 ppm and 6 to 120 ppm, respectively. These concentrations are below 5-day dietary LC_{50} concentrations for avian species tested, indicating a low acute hazard. LC_{50} values for sensitive aquatic species tested indicate dimethoate use would pose a low acute hazard for fish and a moderate hazard for invertebrates.

Use of dimethoate on citrus at recommended use rates would result in initial residues of 10 to 480 ppm on terrestrial wildlife food sources. These concentrations overlap the toxic range for some of the sensitive avian species tested, indicating some hazard. The hazard of acute toxicity to fish appears low, but that for sensitive aquatic invertebrates would be relatively high. In general, of the three uses considered, dimethoate use on citrus appears to present the greatest potential for acute hazard due largely to high application rates and the potential for multiple applications.

An analysis of the comparative toxicity of dimethoate and alternative compounds for use on cotton, alfalfa seed crop, and citrus was made early in the RPAR process. These data were not presented in this document since cancellation is not being considered as a necessary regulatory option. In general, however, it appears that the alternatives would pose an acute hazard to aquatic and terrestrial species tested that is greater than or equal to dimethoate.

III. BENEFIT ANALYSIS OF DIMETHOATE

As part of its regulatory review of dimethoate, the Agency, together with the USDA, has conducted an analysis to determine the economic impact of the possible cancellation of dimethoate. This analysis takes into consideration the availability and cost of alternative chemicals. This analysis will address only those uses identified as important (high exposure/heavy usage) by the USDA/EPA Assessment Team on Dimethoate (1979). Use situations not addressed in this portion of the Position Document will be discussed in Section V. C.

A. Introduction

Annual dimethoate use was estimated at about 2.8 million pounds AI (active ingredient) applied to about 4.7 million agricultural acres. This analysis provides estimates of annual use and economic impacts of a potential cancellation action for the following classes of use sites: grains, field crops, fruits and nuts, vegetables, and other use sites. The economic impacts of the cancellation of dimethoate are summarized in Table V. Major alternative chemicals for each use site are identified in Table VI.

This analysis demonstrates that, in certain instances, the cost of producing a product (crop) will decrease if dimethoate is not available. This apparent decrease in cost to the farmer may be due to several factors:

1) Comparative performance data between dimethoate and alternatives, indicating the quantity and quality of the product, may not have been available for the site under study. In this case the use of an alternative, which may be less

expensive to apply on a per acre basis may result in inferior produce, which in turn would result in lower gross profits for the grower. Because comparative performance data were unavailable, the positive changes in income may reflect a false economy.

2) Alternatives may in fact be more economical than dimethoate; however, growers may be turning to other pesticides slowly.

3) Dimethoate may be used by some growers for other than financial considerations (e.g., acute toxicity, IPM considerations, large inventories of dimethoate, etc.).

B. Grains

Dimethoate use on grains (corn, sorghum, and wheat) accounted for about 792,500 pounds AI applied to about 1.74 million acres (Table V). Less than one percent of the U.S. wheat and corn acres are treated, compared to 7.8 percent for grain sorghum.

For all of the grain use sites, several effective alternatives are available. If dimethoate were cancelled total production costs were estimated to increase $1.03 million for corn and to decrease $0.9 million for sorghum. For wheat, the total production cost changes were qualitatively assessed as minor; alternative controls are less expensive on a per-acre basis ($0.67 and $1.42 less per acre treatment with malathion and parathion respectively).

The lost values of production for corn and sorghum were estimated as $7.8 million and $328,500, respectively. Revenue losses were not estimated for wheat; however, yield losses may result with the use of alternatives, since they are less effective for greenbug control at low temperatures.

The total loss in farm income (changes in costs of production and value of production) for corn producers was estimated as $8.03 million, or $12.52 per impacted acre. For sorghum, the overall impact was a $608,000 increase in farm income or $0.55 per impacted acre; impacts between states, however, were highly variable and ranged from a loss of $3.87 per acre in South Dakota to a gain of $1.63 per acre in Texas. A qualitative evaluation of total farm income effects for wheat indicated a minor impact.

Even though significant economic impacts would be experienced by some grain producers (e.g., $8,000,000 for corn growers), only a small proportion of the total U.S.grain production would be affected. Production impacts due to the cancellation of dimethoate are not expected to affect the economic supply or the final consumers of U.S. grain.

C. Field Crops

Dimethoate use on field crops (safflower, soybeans, cotton, tobacco, and alfalfa) accounted for about 501,000 pounds AI applied to about 1.95 million acres (Table V). Less than one percent of U.S. acreage in soybeans, tobacco, and alfalfa are treated with dimethoate. For U.S. cotton and California and Arizona safflower acreages, 14.6 and 26.0 percent are treated with dimethoate.

For most of the field crops several alternative controls are available. Although no alternative insecticides are available for spider mite control on soybeans, this pest is only a minor and sporadic problem.

If dimethoate were cancelled, total costs of production would increase for safflower ($34,000), cotton ($1.73 million), and tobacco ($5,600). Production costs would decrease by $21,600 for soybeans. A qualitative assessment of cost changes for alfalfa hay (less than a $0.70 to $2.16 per acre increase) or seed (less than a $0.70 to $3.51 per acre increase) indicated negligible effects.

Since there were no losses in production for these field crops, the changes in farm income would be identical to the changes in the costs of production. Estimated farm income effects per impacted acre are -$1.04 for safflower, +$1.27 for soybeans, -$0.71 for cotton, and -$3.48 for tobacco. Farm income effects for alfalfa could not be estimated because of data limitations on use and comparative performance.

Even though significant economic impacts would be experienced by some field crop producers (e.g., $1,726,000 for alfalfa growers, $34,000 for safflower growers, etc.), only a small proportion of the total U.S. grain production would be affected. Production impacts due to cancellation of dimethoate are not expected to affect the economic supply or the final consumers of U.S. grains.

D. Fruits and Nuts

Dimethoate use on fruit and nut crops (apples, pears, citrus, grapes, and pecans) accounted for about 839,000 pounds AI applied to about 533,000 acres (Table V). The percent of total U.S. acreages treated with dimethoate were 2.6 percent for apples, <1.0 percent for pears, 12.0 percent for citrus, and 17.0 percent for pecans. About 50.5 percent of the California grape acreage was treated with dimethoate.

For apples, pears, and pecans several effective alternatives for dimethoate are available; the efficacy and performance of alternatives for grapes and citrus are limited. If dimethoate were cancelled total estimated production cost increases for these crops are $89,700 for apples, $551,000 for citrus, $9.99 million for grapes, and $745,800 for pecans. The minor levels of dimethoate used on pears would have negligible effects upon total production costs.

Changes in the values of production would either be negligible or not expected for apples, pears, and pecans. Annual grape production losses in California, valued at $40,700 are expected from vine losses due to insects commonly referred to as sharp shooters. Significant adverse effects on the quantity and quality of citrus production are possible; however, data were not available to evaluate the economic magnitude of such effects.

Estimated decreased farm incomes for apples and pecans are, respectively, about $90,000 and $745,800 (or $7.00 and $14.34 per impacted acre). For citrus the farm loss could exceed $551,000, or at least $3.58 per impacted acre (significant quality losses due to thrips damage could not be assessed with available data). The decreased farm income for impacted grape producers would be $9.99 million, or $3.83 per acre; total insecticide use would increase. Farm income effects for all pear producers would be negligible; income effects on an impacted acre basis could not be estimated.

Even though significant economic impacts would be experienced by some U.S. fruit and nut producers (e.g., $9,990,000 for grape growers, $745,000 for pecan growers, etc.), consumer impacts are not expected for pears and apples due to the small proportion of the total U.S. production affected. Price increases may occur for pecan, citrus and grape products; but these increases are qualitatively not expected to be of major significance. Consumer impacts could not be quantitatively estimated due to the lack of necessary data.

E. Vegetables

Dimethoate use on vegetable crops (tomatoes, broccoli, beans, peppers, and lettuce) was estimated at about 612,800 pounds AI applied to about 494,700 acres (Table V). The percent of total U.S. acres treated with dimethoate ranged from 7.1 percent for lettuce to 66.2 percent for fresh tomatoes.

Effective alternatives are generally available except for broccoli, fresh snap beans, and fresh tomatoes. If dimethoate were cancelled, increases in total production costs were estimated at about $2.1 million for all of the crops and ranged from a $2.7 million increase for fresh tomatoes to a $371,000 decrease for processing tomatoes. Total production cost changes could not be estimated for lettuce and other vegetables due to biological and usage data limitations. However, the overall change in production costs would be expected to be minor.

For broccoli, the reduction in farm income was estimated at $1.27 million, or $74.15 per acre. Farm income losses for dry, fresh snap beans, and processing snap beans were, respectively, $1.8 million, $3.6 million, and $130,800 (or $6.81, $76.70, and $3.60 per acre). For fresh tomatoes, the total farm income loss was estimated at $3.9 million, or $43.50 per acre.

Since no production losses were estimated for processing tomatoes, the increase in farm income due to less expensive alternative controls would be $371,000, or $12.37 per acre. The overall farm income changes for lettuce and other vegetable crops could not be estimated with available data.

Consumer impacts for fresh snap beans are expected to be minor in the long term because of such factors as: (1) consumers substituting other fresh or processed vegetables in their diets, (2) expanded fresh bean production in other areas, and (3) snap beans designated for the processing market diverting to the fresh market. For broccoli, dry beans, processing snap beans, tomatoes, and lettuce, consumer impacts would qualitatively be either negligible or not expected. Consumer impacts for other vegetable crops could not be estimated due to the lack of necessary data.

F. Other Use Sites

Dimethoate use was investigated on several other use sites which included APHIS quarantine programs (citrus blackfly and hog cholera vector control), livestock premises, forest seed ochards and nurseries, and ornamentals. Total known dimethoate use on these sites may exceed 150,000 pounds AI (Table V).

Dimethoate was not used in 1978 for APHIS quarantine programs, since hog cholera was declared eradicated on January 1, 1978, and since effective control of the citrus blackfly is being achieved with a parasite program. With the hog cholera control program, tetrachlorvinphos + DDVP is a comparably effective alternative for dimethoate. For the citrus blackfly control program, malathion can be substituted for dimethoate at an increased dooryard tree treatment cost of $2.15; if infestations return to the 1974 levels, the total cost increase would be about $234,500.

For adult fly and maggot control in livestock facilities, dimethoate use accounted for 50,600 pounds AI. Several effective alternatives are available at near comparable cost; the production cost increase of alternatives may be as large as $30,900, or $0.44 per 1,000 square feet treated. No adverse agricultural income or consumer price effects are expected.

Known dimethoate use for forest seed orchards and nurseries is limited to 150 acres in the South. Several effective alternatives are available; use of azinphos-methyl would reduce treatment costs by $2.25 to $4.50 per acre. No adverse effects upon producer incomes or consumer prices are expected.

Dimethoate use on ornamentals may approach 50,000 pounds AI with about 90 percent applied commercially and 10 percent used by homeowners. A few site/pest combinations (e.g., camellia/tea scale, boxwood/Comstock mealybug, and juniper/juniper midge) may have pest control problems due to a lack of cost-effective alternatives. However, since most producers grow more than one type of ornamental, any economic impact would probably be of a short term nature until damaged stock was replaced with different varieties. Impacts on consumers are expected to be minor since many substitute ornamental varieties are available in the market.

Table V. Use and Economic Impacts of a Dimethoate Cancellation on Grains

	Dimethoate Use				Economic Impacts				
					Producer Impacts				
Grain Crop	Pounds AI Applied	Acres Treated	Percent of U.S.	Availability of Alternatives	Change in Production Costs	Change in Value Production	Change in Farm Income	Change in Farm Income Per Acre	Consumer Impacts
					thousand dollars			dollars	thousand dollars
Corn	320,000	641,200	<1.0	several	+1,037.0	-6,993.7	-8,030.7	-12.52	none
Sorghum	471,895	1,103,410	7.8	several	- 936.4	- 328.5	+ 607.9	+ .55	none
Wheat	minor; NA	minor; NA	<1.0	several	minor; decrease	minor; NA	minor; NA	NA	none

NA - not available

Table V (continued). Use and Economic Impacts of a Dimethoate Cancellation on Field Crops

	Dimethoate Use				Economic Impacts				
					Producer Impacts				
Field Crop	Pounds AI Applied	Acres Treated	Percent of U.S.	Availability of Alternatives	Change in Production Costs	Change in Value Production	Change in Farm Income	Change in Farm Income Per Acre	Consumer Impacts
					----------thousand dollars		-------------	-dollars------------	-thousand dollars---
Alfalfa	112,500	<300,000	<1.0	several	minor; NA	minor; NA	minor; NA	NA	none
Cotton	362,800	1,600,000	14.6	several	+1,726.5	none	-1,726.5	- .71	none
Safflower	16,282	32,565	26.0; Cal. & Ariz.	several	+ 34.0	none	- 34.0	-1.04	none
Soybeans	8,500	17,000	<1.0	limited	- 21.6	none	+ 21.6	+1.27	none
Tobacco	528	1,600	<1.0	several	+ 5.6	none	- 5.6	-3.48	none

NA - not available

Table V (continued). Use and Economic Impacts of a Dimethoate Cancellation on Fruits and Nuts

	Dimethoate Use				Economic Impacts				
					Producer Impacts				
Fruit or Nut Crop	Pounds AI Applied	Acres Treated	Percent of U.S.	Availability of Alternatives	Change in Production Costs	Change in Value Production	Change in Farm Income	Change in Farm Income Per Acre	Consumer Impacts
					----------thousand dollars		----------------	-dollars------------	-thousand doll
Apples	25,000	13,600	2.6	several	+ 90.0	none	- 90.0	- 7.00	none
Citrus	319,100	153,700	12.0	limited	+ 551.0	potentially[1] significant; NA	>- 551.0	>-3.58	minor overall NA
Grapes	457,048	313,909	50.5; Cal.	limited	+ 9,950	- 40.7	-9,990	-31.83	NA
Pears	negligible; NA	negligible; NA	<1.0	several	negligible; NA	negligible; NA	negligible; NA	NA	none
Pecans	37,630	52,000	17.0	several	+745.8	none	-745.8	-14.34	minor;NA

NA- not available

[1] Potentially significant on affected acres but not immediately indicated.

[2] Minor overall but potentially important for some citrus varities sold for fresh consumption.

Table V (continued). Use and Economic Impacts of a Dimethoate Cancellation on Vegetables

	Dimethoate Use				Economic Impacts				
					Producer Impacts				
Vegetable Crop	Pounds AI Applied	Acres Treated	Percent of U.S.	Availability of Alternatives	Change in Production Costs	Change in Value Production	Change in Farm Income	Change in Farm Income Per Acre	Consumer Impacts
					----------thousand dollars		------------------	-dollars---------	-thousand dollars-
Broccoli	8,600	17,100	26.6	limited	+ 68.0	-1,200.0	-1,268.0	-74.15	negligible
Beans-dry	193,800	258,300	17.2	several	-117.3	-1,877.0	-1,759.7	- 6.81	negligible
-fresh snap	35,500	47,100	51.6	limited	-101.6	-3,714.0	-3,612.4	-76.70	minor in the long run; NA
-processing snap	27,100	36,300	13.0	several	-100.2	- 231.0	- 130.8	- 3.60	negligible

Table V (continued) Use and Economic Impacts of a Dimethoate Cancellation on Vegetables

	Dimethoate Use				Economic Impacts				
					Producer Impacts				
Vegetable Crop	Pounds AI Applied	Acres Treated	Percent of U.S.	Availability of Alternatives	Change in Production Costs	Change in Value Production	Change in Farm Income	Change in Farm Income Per Acre	Consumer Impacts
					----------thousand dollars		------------------	-dollars------------	-thousand dollars--
Lettuce	12,900	16,000	7.1	several	variable; -.4+0 to +121.8	NA	≥ -.4 to +121.8	≥+.02 to -7.57	none
Tomatoes -fresh	237,200	89,400	66.2	limited	+2,689.0	-1,200.0	-3,889.0	-43.50	negligible
-processing	97,500	30,000	9.0	several	-371.0	none	+371.0	+12.37	none
Other vegetables									
-cabbage	NA	NA	NA	several	NA	NA	NA	>-3.87 to +2.77	NA
-peppers	≥150	≥400	NA	several	variable; ≥-2.7 to +1.7	NA	≥-2.7 to +1.7	≥-6.70 to +4.14	NA
-Swiss chard	NA	NA	NA	several	NA	NA	NA	≥-1.05 to +4.37	NA
-turnips	NA	NA	NA	several	NA	NA	NA	>-1.05 to +4.37	NA

NA - not available

Table V (continued). Use and Economic Impacts of a Dimethoate Cancellation on Other Use Sites

	Dimethoate Use				Economic Impacts				
					Producer Impacts				
Other Use Sites	Pounds AI Applied	Units Treated	Percent of U.S.	Availability of Alternatives	Change in Production Costs	Change in Value Production	Change in Income	Change in Income Per Unit	Consumer Impacts
					thousand dollars			dollars	thousand dollars
Citrus blackfly	<1,634	<108,941 tree treatments	NA	limited	<+234.5	none	<-234.5	-2.15 per tree treatment	none
Forest									
-nurseries	100	100 acres	2.1; South	limited	-.4	none	+.4	+4.50	none
-seed orchards	50	100 acres	6.1; South	limited	-.2	none	+.2	+2.25	none
Hog cholera	none	none	none	limited	none	none	none	none	none
Livestock facilities	50,600	69.7 million sq. ft.	<1.0	several	+30.9	none	-30.9	+.44 per 1000 sq. ft.	none
Ornamentals	>50,000	NA	NA	several	NA	NA	NA	NA	minimal; NA

NA - not available

Table VI. Site/Pest Uses of Dimethoate and Alternatives Used In The Economic Analysis

Alfalfa (hay crop)	
aphids	diazinon malathion methyl parathion parathion
leafhoppers	azinphosmethyl (not registered for use in CA) carbaryl malathion methoxychlor
Alfalfa (seed crop)	
aphids	demeton disulfoton methyl parathion
Lygus bug	carbofuran methidathion (Pacific and intermountain states) oxydemeton-methyl (CA only) trichlorfon
Apples (commercial)	
aphids, apple maggot, and codling moth (Midwest and eastern states only)	azinphosmethyl phosalone phosmet
mites (except rust mite)	cyhexatin demeton propargite
Beans (dry)	
aphids	disulfoton malathion parathion
leafminers	parathion
Lygus bug	malathion (CA and NW only) parathion
mites	propargite

Beans (fresh snap)	
aphids	diazinon disulfoton malathion methyl parathion mevinphos parathion
leafminers	diazinon methyl parathion parathion
Lygus bug	carbaryl (CA only) malathion methomyl (CA only) methyl parathion oxydemeton-methyl (CA only) parathion
Beans (snap processing)	
aphids	diazinon disulfoton malathion methyl parathion parathion
leafminers	diazinon methyl parathion parathion
Lygus bug	Carbaryl (CA only) malathion methyl parathion oxydemeton-methyl (CA only) parathion
Broccoli	
aphids	mevinphos oxydemeton-methyl
Cabbage	
aphids	diazinon malathion mevinphos oxydemeton-methyl parathion

Citrus (grapefruit, lemons, oranges and tangerines)	
aphids	demeton (grapefruit, lemons, oranges) malathion mevinphos (grapefruit, lemons, oranges) phosphomidon (tangerines - AZ and CA only) rotenone
thrips	azinphosmethyl diazinon dioxathion formetanate (AZ and CA only) methomyl (AZ and CA only) parathion phosphamidon (tangerines - AZ and CA. only) sulfur
Citrus (Quarantine Programs)	
citrus blackfly	malathion
Corn	
Banks grass mite	disulfoton oxydemeton-methyl propargite parathion
Cotton	
cotton aphids	azinphosmethyl dicrotophos malathion methyl parathion
cotton leafhoppers	dicrotophos malathion methyl parathion trichlorfon
Lygus bug	dicrotophos malathion methyl parathion monocrotophos
spider mites	dicrotophos methyl parathion monocrotophos
thrips	azinphosmethyl carbaryl dicrotophos malathion methyl parathion

Forestry	
Nantucket pine tip moth	azinphosmethyl
Grapes (CA only)	
leafhoppers	carbaryl + ethion
	carbaryl + naled
	carbophenothion
	endosulfan
	ethion
	malathion
	methomyl
	naled
	phosalone
mites	carbaryl + ethion
	carbaryl + naled
	carbophenothion
	endosulfan
	ethion
	malathion
	methomyl
	naled
	phosalone
	propargite
thrips	malathion
	naled
Lettuce	
aphids	demeton
	diazinon
	disulfoton
	endosulfan
	malathion
	mevinphos
	parathion
Livestock premises	
house fly	fenthion
	malathion
	ronnel
	tetrachlorvinphos
	tetrachlorvinphos + DDVP
Pears	
aphids	azinphosmethyl
	carbaryl
	endosulfan
	phosmet

Pears (continued)	
leafhoppers	azinphosmethyl carbaryl
pear psylla	amitraz azinphosmethyl endosulfan oil phosmet
mites (except rust mite)	cyhexatin phosalone
Pecans	
aphids	dialifor disulfoton phosalone
Peppers	
aphids	malathion methomyl oxydemeton-methyl parathion
leafminers and pepper maggot	malathion parathion trichlorfon
Safflower	
Lygus bug	naled
Sorghum	
aphids (incl. greenbugs)	demeton diazinon disulfoton malathion oxydemeton-methyl parathion phorate
Banks grass mite (excl. Trans-Pecos area of Texas)	systox diazinon disulfoton oxydemeton-methyl (SW only) parathion phorate

Soybeans	
Mexican bean beetle	carbaryl
Swiss Chard	
aphids	diazinon malathion parathion
leafminers	malathion parathion
Tobacco	
green peach aphid	acephate diazinon malathion
Turnips	
aphids, leafhoppers and leafminers	diazinon malathion mevinphos parathion
Tomatoes (fresh)	
aphids	methomyl monocrotophos oxamyl (CA and NJ only) parathion
leafminers	monocrotophos parathion oxamyl (FL, SC, AL and CA only)
thrips	parathion
Tomatoes (processing)	
aphids	methomyl parathion
leafminers and thrips	parathion
Wheat	
greenbugs	malathion parathion

IV. Development and Selection of Regulatory Options

A. Introduction

In Sections II and III above, the Agency identified the human and environmental risks associated with the use of dimethoate and identified the benefits associated with each of its uses. As explained in Section I, FIFRA mandates that the Agency achieve a balance between the competing considerations of risks and benefits. In order to accomplish that goal, the Agency has identified various regulatory options and has evaluated each option for its impact on both sides of the risk/benefit equation.

This section of Position Document 2/3 describes the process which the Agency used to develop potential courses of action for evaluation and identifies the options which were ultimately selected for in-depth evaluation. Section V identifies options which the Agency will implement.

B. Basis for the Development of Options

FIFRA provides that the Administrator may cancel the registration of a pesticide whenever he determines that it no longer satisfies the statutory standard for registration which requires (among other things) that the pesticide performs its intended function without "unreasonable adverse effects on the environment" [FIFRA Section 3(c)(5); 7 USC Section 136a(c)(5)]. "Unreasonable adverse effects on the environment" means "any unreasonable risk to man or the environment, taking into account the economic, social and environmental costs and benefits of the use of any pesticide" [FIFRA Section 2(bb); 7 USC Section 136(bb)]. In taking any final action under Section 6(b), the Administrator is required by statute to "consider restricting a pesticide's use or uses as an alternative to cancellation and shall include among those factors to be taken into account the impact of such final action on production and prices of agricultural commodities, retail food prices, and otherwise on the agricultural economy..." [Section 6(b)].

In effect, FIFRA requires the Administrator to weigh the risks and benefits associated with each use of a pesticide. If he determines for any particular use that the risks exceed the benefits, he shall cancel the registration of the pesticide for that use unless he finds that those risks can be sufficiently reduced (so that they are outweighed by the benefits) by the imposition of restrictions upon use through modifications to the terms and conditions of registration (reflected by changes in the labeling) and/or by the classification of the use for restricted use.

The development of regulatory options involves the formulation (and/or modification) of the terms and conditions of registration which are intended to reduce the risks attendant to the use(s) of the pesticide. Each option is then evaluated on a use-by-use basis to determine whether it achieves an adequate reduction in risk without causing unacceptable economic consequences, so that the remaining benefits of the use exceed the remaining risks of that use.

C. Risk Reduction Methods

The development of the regulatory options designed to reduce the risks accompanying the use of dimethoate focused on means to reduce the level of human exposure to dimethoate. In addition to dietary exposure, individuals may be exposed to dimethoate before or during application. Before application, mixers and loaders may be exposed both dermally and via inhalation as the result of splashing, vaporization, or accidental spills; during application, pilots and flaggers involved in aerial application, as well as ground applicators, may all be exposed both dermally and via inhalation.

The Agency has considered each of these exposure situations, and has identified several categories of regulatory options which include various methods of risk reduction. These proposed regulatory options are as follows:

1) Continue registration of all uses without restriction;
2) Continue registration of all uses without restriction but require additional oncogenicity, mutagenicity and delayed neurotoxicity studies;
3) Continue registration of all uses but
   a) require additional oncogenicity, mutagenicity and delayed neurotoxicity studies, and
   b) amend the terms and conditions of certain registrations;

4) Continue registration of all uses but
   a) require additional oncogenicity, mutagenicity and delayed neurotoxicity studies,
   b) amend the terms, and conditions of certain registrations,
   c) require comprehensive studies to determine the amount of exposure incurred during all air blast application situations;
5) Continue the registration of most uses but:
   a) require additional oncogenicity, mutagenicity and delayed neurotoxicity studies,
   b) amend the terms and conditions of certain registrations,
   c) require comprehensive studies to determine the amount of exposure incurred during all air blast situations,
   d) cancel the use of all dust formulations;
6) Continue registration of most uses but
   a) require additional oncogenicity, mutagenicity and delayed neurotoxicity studies,
   b) amend the terms and conditions of certain registrations,
   c) specifically prohibit the use of air blast equipment when treating citrus, pecans, and pome fruits,

d) require comprehensive studies to determine the amount of exposure incurred during all air blast situations not covered in (c) above,

e) specificially warn female workers involved in air blast application practices of the potential teratogenic effects of dimethoate,

f) cancel the use of all dust formulations;

7) Cancel all uses.

The risks and benefits of each of the above options are described below.

(1) Option #1

Continue registration of all uses without restrictions

Adopting Option 1 would indicate that the Agency concludes that the benefits associated with each use outweigh the respective risks and that therefore none of the uses of dimethoate cause unreasonable adverse effects. This option would return pesticide products which contain dimethoate to the registration process, would not reduce the mutagenic or reproductive/teratogenic risks associated with the use of dimethoate, would not result in any adverse economic impact and would retain the use of dimethoate. The choice of this option would indicate that the Agency is willing to tolerate a level of risk greater than the levels of risk estimated for other options in order to retain the highest possible benefits.

(2) Option #2

Continue registration of all uses without restriction but require additional oncogenicity, mutagenicity and delayed neurotoxicity studies

Adopting Option 2 would indicate that the Agency concludes that the benefits associated with the use of dimethoate outweigh potential risks based on available studies. This option, however, indicates that the Agency requires additional testing and indicates a desire on the part of the Agency to reevaluate the oncogenicity and mutagenicity risk picture when these new data are available. This option would not reduce mutagenic or reproductive/ teratogenic risk in the short run as discussed in Section III. This option would not result in any adverse economic impacts and would retain the use of dimethoate as currently registered.

(3) Option #3

Continue registration of all uses but

a) require additional oncogenicity, mutagenicity and delayed neurotoxicity studies, and

b) amend the terms and conditions of certain registrations.

Adopting Option 3 would indicate that the Agency concludes that potential risks are too high relative to the benefits associated with the use of dimethoate. This option, however, would indicate that benefits of dimethoate use would outweigh risks if specific changes in application practices were implemented. In addition, this option would indicate the Agency's conclusion that additional data concerning the oncogenic and mutagenic potential of dimethoate are required. Implementation of this option would reduce risks to acceptable levels (Table VII and VIII) without substantial adverse economic impacts. Modifications that would be implemented under this option fall into three major categories, discussed in detail below:

1) Require protective clothing for all formulations and all uses,
2) Require respirators for pilots and mixer/loaders, and
3) Require automatic flagging for all aerial application situations.

(a) Require Protective Clothing For All Products and All Uses

This modification is intended to reduce risk by reducing dermal exposure. The protective clothing would consist of wide brimmed hats, impermeable gloves, rubber or synthetic rubber boots or boot covers, long-sleeved shirt and long pants made of a closely woven fabric. This protective clothing would be worn by all applicators, including homeowners, and by all personnel involved with mixing, loading, transferring, or otherwise handling this pesticide.

In calculating dermal exposure to dimethoate the Agency assumed that 10% of the dimethoate coming into contact with skin will be absorbed and that 15% of the total body surface (approximately 1.8 m^2) will be exposed, or about 2000 cm^2. For purposes of calculating dermal exposure, the Agency assumes that the amount of dimethoate absorbed will be reduced five-fold (Severn unpublished) when protective clothing is used.

Applicators are exposed to dimethoate orally (i.e., through food) in addition to the dermal and inhalation routes of exposure. As discussed in Section II.C.(3)(b)(i) the MOS resulting from oral exposure alone was 875 (probable case). This MOS is likely to be an overestimate of the true oral exposure picture in that this figure was derived assuming dimethoate residues to be present at tolerance levels. The Agency used tolerance levels in calculating exposure due to a lack of data concerning actual residues at harvest. It is generally recognized, however, that organophosphorous pesticides such as dimethoate degrade rather rapidly and that actual residues at harvest are many orders of magnitude lower than tolerance levels. In calculating applicator exposure this artifically high oral exposure value was added to anticipated occupational exposure in calculating margins of safety for teratogenic effects. This addition of artifically high oral exposure values has the effect of artifically increasing total applicator exposure. Table III, for example, indicates that the oral exposure is over 65% of the total exposure for pilots spraying cotton, 92% of total exposure for mixer/loaders involved in the application (ground) of dimethoate to lettuce, etc.

This additive contribution of the oral component also has the effect of masking the risk-reducing effect of regulatory options on risk. If 92% of the exposure theoretically results from the oral route (mixer/loader for lettuce) it is obvious that, even though regulatory options such as protective clothing eliminate a large portion of the 8% non-oral exposure (worker exposure), this reduction in worker exposure does not significantly affect the MOS for teratogenic effects (because the majority of the exposure results from the additive effect of an artifically high oral exposure value).

Therefore, in order to evaluate the risk-reducing effect of the various options, the Agency calculated margins of safety for teratogenic effects resulting from worker exposure separately from that of worker exposure combined with oral exposure. In this way the risk-reducing effects of the various regulatory options can be observed without the masking influence of artifically high oral exposure. Table VII shows MOS values for various activities and the effect of each regulatory option without the oral exposure values. For example, unprotected workers involved in the ground application of dimethoate (custom applicators) to grapes have a MOS of 135. The MOS for these workers when protective clothing is required increases to 467. If the

Table VII

APPLICATOR EXPOSURE AND MARGINS OF SAFETY FOR VARIOUS USERS OF DIMETHOATE
Excluding Dietary (oral) Exposure

CROP	TYPE OF SPRAYING	SUBGROUP	COMBINED DERMAL AND INHALATION EXPOSURE	MOS UNDER CURRENT PRACTICES (1)	EXPOSURE (DERMAL AND INHALATION) WHEN PROTECTIVE CLOTHING IS REQUIRED	MOS WHEN PROTECTIVE CLOTHING IS REQUIRED	TOTAL EXPOSURE WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED	MOS WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED
corn	air	pilots	0.0083	337	0.00806	347	0.00086	3,256
corn	air	flaggers	0.008	350				
corn	air	mixer/loader	0.0063	444	0.0043	651	0.00088	3,182
ornamental	ground	commercial high concentration compressed air	0.00012	23,333	0.000037	75,676	0.00002	140,000
ornamental	ground	home garden high concentration	0.000152	18,421	0.000045	62,222	0.00003	93,330
grape	ground	boom highest conc.	0.0012	2,333	0.0004	7,000	0.00023	12,174
grape	ground	highest conc. (custom) copplestone model	0.0207	135	0.006	467	0.0038	737
grape	ground	dust	0.130	22[2/]	0.130	22	0.013	215
cotton	air	pilot	0.0017	1,647	0.0016	1,750	0.00017	16,471

(1) Based on a 2.8 mg/kg NOEL (Khera unpublished)
(2) Exposure is via inhalation

Table VII (continued)

APPLICATOR EXPOSURE AND MARGINS OF SAFETY FOR VARIOUS USERS OF DIMETHOATE
Excluding Dietary (oral) Exposure

CROP	TYPE OF SPRAYING	SUBGROUP	COMBINED DERMAL AND INHALATION EXPOSURE	MOS UNDER CURRENT PRACTICES (1)	EXPOSURE (DERMAL AND INHALATION) WHEN PROTECTIVE CLOTHING IS REQUIRED	MOS WHEN PROTECTIVE CLOTHING IS REQUIRED	TOTAL EXPOSURE WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED	MOS WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED
cotton	air	mixer/loader	0.0095	295	0.00065	4,308	0.00014	20,000
cotton	ground	applicators	0.0078	359	0.0024	1,167	0.00145	1,931
cotton	ground	mixer/loader	0.00033	8,485	0.00011	25,454	0.00007	40,000
citrus	air	pilot ground crew mixer/loader	same as corn					
citrus	ground (air blast model)	applicators (2) mixer/loader	0.39	7	0.078	36	0.071	39
sorghum	air	same as corn						
veg. fields (tomato, broccoli	air	pilot flaggers mixer/loader	0.013 0.013 0.0062	215 215 452	0.0128 0.0043	219 651	0.014 0.00088	2,000 3,182
veg. (Fla.)	ground	applicator	0.00005	56,000	0.00001	280,000	0.000007	400,000
vector control (house fly)	ground	applicator	0.0019	1,474	0.0009	3,111	0.00032	8,750

(2) Applicator is also mixer/loader

Table VII (continued)

APPLICATOR EXPOSURE AND MARGINS OF SAFETY FOR VARIOUS USERS OF DIMETHOATE
Excluding Dietary (oral) Exposure

CROP	TYPE OF SPRAYING	SUBGROUP	COMBINED DERMAL AND INHALATION EXPOSURE	MOS UNDER CURRENT PRACTICES (1)	EXPOSURE (DERMAL AND INHALATION) WHEN PROTECTIVE CLOTHING IS REQUIRED	MOS WHEN PROTECTIVE CLOTHING IS REQUIRED	TOTAL EXPOSURE WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED	MOS WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED
forest pine (seed orchard)	ground	applicator	0.0008	3,500	0.00025	11,200	0.00014	20,000
pecan high conc.	ground (air blast model)	applicator (2) mixer/loader	0.119	24	0.0252	111	0.0232	121
safflow	air	same as corn						
pome	ground (air blast model)	commercial applicator including mixer/loader	0.242	12	0.0527	53	0.0485	58
pome	ground	hose sprayer	0.00017	16,471	0.00005	56,000	0.000032	87,500
soybean	air	same as corn						
wheat	air	same as corn						
tobacco high conc.	ground	applicator including mixer/loader	0.00042	6,667	0.00013	21,538	0.00008	35,000
alfalfa high conc.	ground	applicator including mixer/loader	0.0052	538	0.00163	1,718	0.00097	2,887

(2) Applicator is also mixer/loader

Table VII (continued)

APPLICATOR EXPOSURE AND MARGINS OF SAFETY FOR VARIOUS USERS OF DIMETHOATE
Excluding Dietary (oral) Exposure

CROP	TYPE OF SPRAYING	SUBGROUP	COMBINED DERMAL AND INHALATION EXPOSURE	MOS UNDER CURRENT PRACTICES (1)	EXPOSURE (DERMAL AND INHALATION) WHEN PROTECTIVE CLOTHING IS REQUIRED	MOS WHEN PROTECTIVE CLOTHING IS REQUIRED	TOTAL EXPOSURE WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED	MOS WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED
veg. fields (lettuce	ground	applicator	0.0002	14,000	0.00007	40,000	0.000043	65,116
		mixer/loader	0.00026	10,769	0.00009	31,111	0.000054	51,852

Table VIII

APPLICATOR EXPOSURE AND MARGINS OF SAFETY FOR VARIOUS USERS OF DIMETHOATE
Including Dietary (oral) Exposure

CROP	TYPE OF SPRAYING	SUBGROUP	COMBINED DERMAL AND INHALATION EXPOSURE WHEN PROTECTIVE CLOTHING IS REQUIRED	ORAL EXPOSURE	TOTAL EXPOSURE	MOS WHEN PROTECTIVE CLOTHING IS REQUIRED	TOTAL EXPOSURE WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED	MOS WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED
corn	air	pilots	0.00806	0.0032	0.0113	248	0.00406	690
corn	air	flaggers	-	-	-	-	-	-
corn	air	mixer/loader	0.0043	0.0032	0.0075	373	0.00408	686
ornamental	ground	commercial high concentration compressed air	0.000037	0.0032	0.0033	865	0.00322	870
ornamental	ground	home garden high concentration	0.000045	0.0032	0.00325	862	0.00323	867
grape	ground	boom highest concentration	0.0004	0.0032	0.0036	778	0.00343	816
grape	ground	highest concentration (custom) Copplestone model	0.006	0.0032	0.0092	286	0.007	400
grape	ground	dust	0.130	0.0032	0.1332	21	0.0162	173
cotton	air	pilot	0.0016	0.0032	0.0048	583	0.00337	831
cotton	air	mixer/loader	0.00065	0.0032	0.0039	718		
cotton	ground	applicators	0.0024	0.0032	0.0056	500	0.00334	838

Table VIII (continued)

APPLICATOR EXPOSURE AND MARGINS OF SAFETY FOR VARIOUS USERS OF DIMETHOATE
Including Dietary (oral) Exposure

CROP	TYPE OF SPRAYING	SUBGROUP	COMBINED DERMAL AND INHALATION EXPOSURE WHEN PROTECTIVE CLOTHING IS REQUIRED	ORAL EXPOSURE	TOTAL EXPOSURE	MOS WHEN PROTECTIVE CLOTHING IS REQUIRED	TOTAL EXPOSURE WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED	MOS WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED
cotton	ground	mixer/loader	0.00011	0.0032	0.0033	848	0.00327	856
citrus	air	pilot groung crew mixer/loader	same as corn					
citrus	ground (air blast)	applicators (1) mixer/loader	0.078	0.0032	0.081	35	0.0742	38
sorghum	air	same as corn						
veg. fields (tomato, broccoli)	air	pilot flaggers	0.0128	0.0032	0.16	175	0.0046	609
		mixer/loader	0.0043	0.0032	0.0075	373	0.00321	872
veg. (Fla.)	ground	applicator	0.00001	0.0032	0.0032	875	0.00408	686
vector control (house fly)	ground	applicator	0.0009	0.0032	0.0041	683	0.00352	795
forest pine (seed orchard)	ground	applicator	0.00025	0.0032	0.0035	800	0.00334	838
pecan high concentration	ground (air blast)	applicator (1) mixer/loader	0.0252	0.0032	0.0284	99	0.0264	106

(1) Applicator also does mixing/loading

Table VIII (continued)

APPLICATOR EXPOSURE AND MARGINS OF SAFETY FOR VARIOUS USERS OF DIMETHOATE Including Dietary (oral) Exposure

CROP	TYPE OF SPRAYING	SUBGROUP	COMBINED DERMAL AND INHALATION EXPOSURE WHEN PROTECTIVE CLOTHING IS REQUIRED	ORAL EXPOSURE	TOTAL EXPOSURE	MOS WHEN PROTECTIVE CLOTHING IS REQUIRED	TOTAL EXPOSURE WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED	MOS WHEN PROTECTIVE CLOTHING AND RESPIRATORS ARE REQUIRED
safflower	air	same as corn						
pome	ground (air blast model)	commercial applicator including mixer/loader	0.0527	0.0032	0.0559	50	0.0517	54
pome	ground	home sprayer	0.00005	0.0032	0.0033	861	0.00323	867
soybean	air	same as corn						
wheat	air	same as corn						
tobacco high conc.	ground	applicator including mixer/loader	0.00013	0.0032	0.0033	848	0.00328	854
alfalfa high conc.	ground	applicator including mixer/loader	0.00163	0.0032	0.0048	583	0.00417	671
veg. fields (lettuce)	ground	applicator	0.00007	0.0032	0.0033	848	0.00324	864
		mixer/loader	0.00009	0.0032	0.0033	848	0.00325	862

oral exposure complement for this same worker wearing protective clothing is added the MOS drops to 286 (Table VIII). This MOS of 286, therefore, is artifically low and does not accurately reflect risk nor does it reflect the risk-reducing effects of regulatory options. The effect of regulatory options on the MOS for each use situation, therefore, is calculated twice, first without the oral exposure complement (Table VII) and secondly with the oral exposure complement (Table VIII).

Even though there is some risk from dietary exposure, it is likely that MOS figures in Table VII most accurately reflect total risk (MOS) for application and that figures in Table VIII are overestimated.

In the case of protective clothing, increased production costs of dimethoate-treated commodities or other economic impacts would not be expected (memo 1979e) because applicators commonly own or wear the required protective clothing.

(b) Require Respirator For Pilots and Mixer/Loaders

In calculating respiratory exposure the Agency assumed 100% of the dimethoate entering the lungs would be absorbed. For purposes of calculating the decrease in exposure and concurrent risk reduction afforded by respirators, the Agency assumes that proper respiratory protective devices will reduce the inhalation exposure by 90% (Severn unpublished). Application situations requiring respirators will be those of pilots and mixer/loaders for whom margins of safety are shown in tables VII and VIII. As was the case with protective clothing, MOS figures are calculated twice; once including oral exposure (Table VIII) and once without the oral complement (Table VII). Pilots would not be required to wear respirators when their planes are equipped with positive ventilation equipment.

The economic impact of requiring applicators to wear respirators capable of removing particulate matter (e.g. canister type) would be negligible. Custom applicators would be expected to have such equipment at present; hence no additional investment costs would be required on the part of custom applicators (memo 1979e).

(c) Require Automatic Flagging For All Aerial Application Situations

Flaggers are individuals stationed at predetermined points in a field who indicate to pilots applying dimethoate where to begin (or stop) applying the pesticide. As a result these individuals can come into direct contact with the pesticide and are at risk as indicated in Table II. This modification is intended to eliminate risk by requiring the use of automatic flagging equipment. Automatic flaggers are small mechanical devices mounted on the aircraft which dispense a marker which the pilot can use to mark the beginning and/or end of the swaths. These devices eliminate the need for flaggers and therefore eliminate the risk to this segment of the population. The economic impact of requiring automatic flagging equipment would be minor. The relative cost of using automatic flagging versus conventional flagging (human flaggers) would be dependent upon several factors such as: 1) topography, 2) level of application accuracy desired, 3) field acreage, and 4) field dimension.

Several types of automatic flagging devices that use biodegradable paper, smoke, or other marking methods are available. Flagging devices using bio-degradable paper flags retail for $395.00; a case of 400 flags retails for $42.00 or $0.11 per flag. One to five flags are used per swath, depending on the terrain and desired accuracy of application (memo 1979a).

Given the low investment and operating costs associated with automatic flagging equipment, the custom applicator may be able to reduce costs by adopting flagging rather than the more conventional methods. Current labor costs per worker for conventional flagging may range from $4 to $5 per hour and workers may not be available when needed.

In conclusion, negligible economic impacts are associated with implementing automatic flagging for dimethoate both at the production and consumption levels.

(4) Option #4

Continue registration of all uses but

a) require additional oncogenicity, mutagenicity and delayed neurotoxicity studies;

b) amend the terms, and conditions of certain registrations, and

c) require comprehensive studies to determine the amount of exposure incurred during all air blast application situations.

Adopting Option 4 would indicate that the Agency concludes that benefits associated with the use of dimethoate outweigh potential risks when specific application practices are implemented as discussed in Option 3. This option indicates that the Agency desires to evaluate its position when additional data are available on air blast application techniques. This option indicates that there is insufficient exposure data concerning air blast application situations to determine whether margins of safety for reproductive/teratogenic effects do in fact fall in the range of 39-121 as discussed in section III (Table VII). This option would not reduce risk beyond that resulting from the implemention of specific application practices as discussed in Option 3. This option would not result in any adverse economic impacts and would retain the use of dimethoate as currently registered.

(5) Option #5

Continue registration of most uses but

a) require additional oncogenicity, mutagenicity and delayed neurotoxicity studies,

b) amend the terms and conditions of certain registrations, and

c) require comprehensive studies to determine the amount of exposure incurred during all air blast situations;

d) cancel the use of all dust formulations.

Adopting Option 5 would indicate that the Agency concludes that benefits associated with most uses of dimethoate outweigh potential risks when specific changes in application practices are implemented. This option would encompass all the changes in application practices discussed in Option 3 (protective clothing, respirators, and automatic flagging), and would provide for the gathering of comprehensive information concerning applicator exposure during air blast application as discussed in Option 4. This option would permit dimethoate to be applied using air blast equipment while exposure information is being gathered.

Option 5 goes on to indicate that the Agency concludes that risk resulting from the use of dust formulations of dimethoate outweigh benefits derived from the use of dust formulations.

Cancellation of dimethoate dust on grapes would have no economic impacts at the producer or consumer levels because the dimethoate wettable powder formulation is more widely used on grapes and would be expected to replace the dust formulation for this crop use. No adverse effects on the quantity or the quality of grape production are expected (memo 1979e).

Dimethoate dust formulations are also registered for use on potatoes; however, very little of the dust formulation is used (Waugh, memo). Other formulations of dimethoate are available for this use and no adverse economic effects are expected from its cancellation (Memo 1979e).

(6) Option #6

Continue the registration of most uses but,

a) Require additional oncogenicity, mutagenicity and delayed neurotoxicity studies,

b) Amend the terms and conditions of certain registrations, and

c) Specifically prohibit the use of air blast equipment when treating citrus, pecans, and pome fruits,

d) Require comprehensive studies to determine the amount of exposure incurred during all air blast situations not covered in (c) above,

e) Specifically warn female worker involved in air blast application practices of the potential teratogenic effects of dimethoate,

f) Cancel the use of all dust formulations

Adopting Option 6 would indicate that the Agency concludes that benefits associated with most uses of dimethoate outweigh potential risks when specific changes in application practices are implemented (protective clothing, respirators, automatic flagging). This option would encompass all the changes in application practices discussed in Option 3, but would go on to specifically prohibit the use of air blast application equipment when treating citrus, pecans, and pome fruits (apples and pears). This option indicates that in the case of citrus, pecans, and pome fruits, available protective equipment will not reduce the risk experienced by applicators using air blast equipment to an acceptable level (Table VII). This option goes on to indicate that the Agency concludes that the risk resulting from the use of dust formulations of dimethoate outweigh benefits derived from the use of dust formulations. In addition, this option specifies the Agency's requirement for additional applicator exposure data concerning air blast application practices other than citrus, pecan and pome fruits. Option 6 would permit the use of air blast equipment (for crops other than citrus, pome fruits and pecans) while air blast exposure information is being gathered.

Option 6, however, would go on to state the Agency's concern for women applicators applying dimethoate via air blast equipment during pregnancy. Under Option 6 the Agency would require all products containing dimethoate which can be or are intended to be used with air blast equipment to bear the following warning:

> "Warning to Female Workers" (16 pt. Red lettering)
> The United States Environmental Protection Agency has determined that dimethoate, an active chemical ingredient in this product, causes birth defects in laboratory animals. Exposure to this product during pregnancy should be avoided.

For products which are not intended for use with air blast equipment the following statement shall appear on all labeling:

> "Warning (16 pt. Red lettering)
> Do not use this product with Air Blast Equipment."

Adopting Option 6 would indicate, as does Option 5, that the Agency concludes that risks resulting from the use of dust formulations of dimethoate outweigh benefits derived from the use of dust formulations. Option 6 would decrease applicator risk as discussed in Option 3 and would eliminate risk resulting from the use of dust formulations and of air blast application on citrus, pecans and pome fruits. This option would not result major economic impacts and would retain most dimethoate use patterns.

In determining whether to prohibit the use of air blast equipment or cancel dust formulations, the Agency must evaluate the potential human risk posed by alternative chemicals, or alternative formulations of dimethoate. As discussed below, air blast applicators may switch to alternative chemicals rather than apply dimethoate by other application methods (e.g. boom, hydraulic equipment or by air).

The potential risk posed by alternative pesticides will be discussed separately for each crop as well as for dust formulations.

Citrus

The use of dimethoate on citrus is limited, for the most part, to Arizona and California. Approximately 46% of the citrus acres in Arizona and California are treated with dimethoate. In both states thrips is the primary pest although aphids are also a problem. The major alternatives to dimethoate use on citrus are formetanate, malathion, phosphamidon, demeton and mevinphos (USDA/EPA 1979). None of these pesticides have identifiable adverse chronic or delayed toxic effects, although a complete data base is lacking for many of these compounds. Available data (memo 1979h) indicate that these major alternatives do not appear more hazardous than dimethoate.

Pome Fruits (Apples and Pears)

In the case of apples dimethoate is primarily used to control aphids and mites. Only 2.6% of the total U.S. apple acres are treated with dimethoate (USDA/EPA 1979). If growers were to switch to alternative pesticides, azinphosmethyl, cyhexatin, propargite and demeton would be the compounds of choice. Available data (memo 1979h) indicates that, with the exception of azinphosmethyl which is under review, these major alternatives do not appear more hazardous than dimethoate.

Azinphosmethyl is more acutely toxic than dimethoate and, based on a recent National Cancer Institute study, may pose a carcinogenic risk (memo 1979h). However, because only 2.6% of apple acres are treated with dimethoate, any incremental risk due to the use of azinphosmethyl as a substitute is assumed to be insignificant. Moreover, azinphosmethyl is a restricted use pesticide and can only be used by trained pesticide applicators.

Available pesticide usage surveys indicate no use of dimethoate on pears in recent years (USDA/EPA 1979). Because dimethoate is not used on pears, prohibiting the use of airblast application practices would not result in increased risk due to alternatives.

Pecans

Dimethoate is most often applied to pecans to control aphids. The primary alternatives to dimethoate for use on pecans are phosalone and dialifor. Phosalone is slightly more acutely toxic than dimethoate. Agency records indicate that phosalone has been tested for oncogenicity, delayed neurotoxicity, reproductive and teratogenic effects with negative results. Dialifor is more acutely toxic than dimethoate and has under gone the same tests as phosalone with negative results. The vast majority of toxicity data supporting dialifor, however, was carried out at Industrial Bio-Test and these data have not been validated. Therefore, conclusions concerning the reliability of these data cannot be made at this time.

Dimethoate is not of great importance for pecans in that phosalone is the most popular compound for aphid control (USDA/EPA 1979). Although the validity of the data concerning dialifor is in question, phosalone and dialifor do not appear to be more hazardous than dimethoate.

Dust Formulations

Dimethoate dust formulations are used on grapes and to a very minor degree on potatoes. Dimethoate in the form of a wettable powder is the alternative compound/formulation of choice for grapes and pototoes. Because the wettable powder formulation results in lower applicator exposure, the total risk for the wettable powder formulation would be less than that of the dust formulation.

The economic impact of precluding airblast application practices differ for each crop and will be discussed separately.

(a) Citrus

Of the 245,000 dimethoate acre-treatments applied to citrus annually, about 69,900 (29%) and 175,300 (71%) are applied by air and ground equipment, respectively. This restriction would impact upon those users applying dimethoate by ground equipment, most of which are believed to be air-blast treatments.

Restrictions of air-blast application would leave users with three application method alternatives: 1) aerial 2) oscillating booms, or 3) manually operated hydraulic guns. Crew size, exposure time, and man-hour requirements for these methods and for air-blast are as follows:

	crew size	exposure time/acre	man-hours/acre required for application
air-blast	2	15 minutes	0.5
aerial	3	1 minute	0.05
oscillating boom	3	15 minutes	0.75
manual spraying	4	1.5 hours	6.0

The use of oscillating boom sprayers or manually operated hydraulic pressue guns for citrus thrips control is both inappropriate and prohibitively expensive. These application methods are used for pest control requiring "thorough coverage" high gallonage (more than 1,000 gallons spray per acre) treatments in which all interior and exterior parts of the tree are wetted by the spray material. The cost of thorough coverage treatment runs from $40 to $50 per acre depending upon citrus type, tree size, and specific application method used. Aphid and thrip control generally involve a mist spray application of pesticide since only the outside or peripheral parts of the tree require treatment. The cost of mist spray application using air blast sprayers (100 - 500 gallons spray/acre) averages about $20 per acre. Thus, oscillating booms and manual spraying are generally ruled out for dimethoate use on citrus because of expense and the lack of fit of these methods for aphid and thrip control.

Aerial application, an alternative to air-blast ground equipment, is in widespread practice. Aerial application is less expensive than air-blast application, averaging about $5-$10 per acre compared to $20 per acre for air-blast. Based on cost alone it would seem logical to assume that all citrus applications of dimethoate could be performed by air. However, aerial applications are limited by two factors:

1) effectiveness - air-blast treatments are more effective than aerial when moderate to heavy pest infestations are present.

2) capacity - it is doubtful whether available aircraft could handle all the acreage requiring treatment, at least in the short run.

It is safe to conclude that aerial application could replace ground sprayers in some or many instances. However, it would be inappropriate to assume that all ground applications of dimethoate on citrus could be replaced by aircraft due to the treatment effectiveness and equipment availability factors outlined above. Some dimethoate users would use aerial application, a few might switch to ground application techniques other than air-blast sprayers, and some would use alternate insecticides. Because of a lack of data at present it is not possible to predetermine the relative adoption ratios of these three strategies and their associated economic impacts. Thus, impact of restricting air-blast application could range from zero impact to the same impact as cancellation ($551,000/year) [USDA/EPA 1979 memo 1979f].

(b) Pome Fruit

Unlike citrus, only small acreages of apples and pears receive aerial pesticide applications. Although dimethoate is registered for aerial application on apples and pears, growers rely almost exclusively on ground equipment, particularly air-blast equipment, for pest control. As in citrus, apple and pear growers prefer not to use large quantities of water when spraying in order to minimize sprayer travel and refill time, to avoid soil compaction, etc.

Due to the high cost of ground application methods other than air blast, if ground application of dimethoate were prohibited on apples and pears, current dimethoate users would probably utilize alternative pesticides. The economic effect would likely be equivalent to the cancellation impacts (about $90,000 per year) [memo 1979f].

(c) Pecans

Approximately 1,430 farms currently produce pecans on 52,000 acres with two dimethoate applications per year. Approximately 90% of these acres were treated with ground equipment. If air blast application were not permitted growers would either purchase hydraulic sprayers with which to apply dimethoate, at a cost of approximately $3000 or use some alternative pesticide.

If hydraulic equipment was purchased and assuming a seven year economic life, annual investment costs would not be expected to exceed $650 per year for each farmer (memo 1979d). The operating costs per acre would also increase with hydraulic sprayer because 1) fewer acres can be treated per hour with hydraulic equipment (2 acres/hour) than with air blast equipment (4-5 acres/hour), and 2) larger work crews are required (one worker for air blast equipment compared to three workers for hydraulic systems). Under these conditions the anticipated increase in investment and operating costs per grower would be approximately $1082.00 and up to $1.4 million for all growers.

Based on existing information on the performance and costs of available alternatives, as well as the problem of farm labor shortage, few producers of pecans would be expected to invest in hydraulic spray equipment. Therefore, this regulatory option would have the same result as a dimethoate cancellation ($745,999) for many of the impacted producers.

(7) Option #7

Cancel All Uses

Adopting Option 7 would indicate that the Agency concludes that the risks associated with all of the uses outweigh the respective benefits and thereby result in unreasonable adverse effects. This option would eliminate all of the uses of dimethoate. Cancellation would eliminate all of the reproductive/teratogenic and mutagenic risks associated with the use of dimethoate (Table III), but at a cost to growers of $8 million per year for corn, $10 million dollars per year for grapes, and 3.9 million dollars for fresh tomatoes. Additional losses for other commodities are also expected (Table IV). The choice of this option would indicate that the Agency is unwilling tolerate the level of risk associated with any use of dimethoate.

V. RECOMMENDED OPTIONS

A. Comparison of Options

In selecting a regulatory option, the Agency must decide which of the proposed options achieves the most appropriate balance between risks and benefits. This decision turns in part on the key factual elements summarized above, and in part on the relative merits of each proposed option.

Option 1 (which would continue the registration for all uses) and Option 7 (which would cancel the registration for all uses) represent all or nothing approaches to regulating. By adopting Option 1, the Agency would not reduce the potential risks, nor would it otherwise recognize that the RPAR review confirmed the presumption of mutagenicity and reproductive/ teratogenic effects. Option 1 would be reasonable only if the benefits clearly outweigh the risks, and if reductions in risk cannot be achieved without unacceptable impact on the benefits. Option 7 would be reasonable only if the risks clearly outweigh the benefits, and if significant reductions in risks cannot be achieved by measures short of cancellation without unacceptable impacts on the benefits. A review of the data indicates that neither situation prevails and that alternative options are available which are environmentally and economically sound. Therefore, Options 1 and 7 are not reasonable regulatory measures in this case.

Option 2 provides a mechanism for the development of additional information concerning oncogenicity and teratogenicity. This option, like Option 1, fails to reduce potential risk from mutagenic and reproductive/ teratogenic effects. Because other options are available which will reduce risk without adverse economic impacts, Option 2 is not acceptable.

Option 3 goes beyond the information-gathering process discussed in Option 2 and focuses on methods of reducing exposure to applicators. Option 3 is preferable to Option 2 in that it delineates specific requirements intended to reduce applicator risk. These risk-reducing requirements (e.g., protective clothing, respirators, automatic flagging) are particularly appealing in that the requirements have so little economic impact. This option does not, however, address the high risk air blast application situations nor the risk resulting from the use of dust formulations. Because other options are available which will either reduce risk in these areas without significant economic impact or will produce additional data with which to evaluate risk, Option 3 is not acceptable.

Option 4 encompasses all the risk-reducing characteristics contained in Option 3 but goes on to indicate that the air blast method of application results in comparatively high exposure and risk. This option indicates that additional studies are needed to accurately determine the amount of exposure incurred during air blast application. This option concludes that the benefits derived from the use of air blast equipment outweigh risks and that air blast equipment may be used while exposure related information is being gathered. This option fails, as does Option 3, to reduce risk due to air blast application techniques, due to dust formulations nor does Option 4 warn female applicators of potential teratogenic danger resulting from air blast application practices. Because other options are available which will reduce risk and which will warn applicators of or eliminate risk from air blast application without significant economic impact, Option 4 is not acceptable.

Option 5 differs from Option 4 in that the selection of Option 5 would result from the conclusion that risks resulting from the use of dust formulations outweigh potential benefits. Option 5, however, fails to make provisions for reducing risk associated with selected high risk air blast application situations. Because another option is available which provides additional reduction in risk, without significant economic impact, Option 5 is not acceptable.

Option 6 differs from Option 5 in that Option 6 eliminates three specific use situations (citrus, pome fruits, and pecans) where applicator risk is unacceptably high in light of the benefits derived from this use and provides for precautionary labeling to inform female applicators of potential teratogenic hazard resulting from other air blast application practices rather than eliminating this method of application altogether. Option 6 maintains the majority of the economic benefits derived from the use of dimethoate. Under Option 6 the decision to permit some air blast application methods is an interim decision, and will be reevaluated when additional air blast exposure data becomes available.

B. Recommended Options

The Agency recommends adoption and implementation of regulatory option number 6. Option 6 is selected because it represents the best available course of action for reducing or eliminating applicator exposure and concurrent risk while maintaining a generally high level of benefits and for gathering additional toxicological data needed to better evaluate risk. In adopting Option 6, the Agency is proposing to take regulatory action in three general areas: 1) generation of additional data; 2) modifying the terms and conditions of registration for the uses of dimethoate; and 3) cancellation of selected high risk application practices and high risk formulations.

1) Generation of additional data

Option 6 identifies data gaps in the areas of chronic health studies and worker exposure. The option provides a mechanism for the generation of additional oncogenicity, mutagenicity, neurotoxicity and exposure data, as discussed in Section VI, in a timely manner for a reassessment of human risk if this additional data indicates such a reassessment to be necessary.

2) Altering selected application practices

Option 6 identifies selected application practices which result in comparatively high risk, and proposes specific changes in the terms and conditions of registration to modify the practices and product labeling which have the effect of reducing risk to acceptable levels without significant impact upon benefits.

3) Cancellation of selected high risk application practices and formulations

Option 6 identifies specific air blast application situations (citrus, pome fruits and pecans) and formulations (dusts) which result in unacceptably high exposure and consequent risks.

C. Use Situations not Addressed In This Analysis

Dimethoate is used in a variety of situations not analyzed in this position document, such as minor and specialty crop uses, general fly control, etc. The USDA/EPA Assessment Team on Dimethoate did not identify these as major/high volume uses nor as uses resulting in high worker exposure. Because these are minor/low volume uses of dimethoate the Agency assumes that comparatively few individuals will be exposed and those who are exposed will be exposed to relatively low levels of dimethoate and, therefore, will experience low risk.

The Agency makes this assumption based on the exposure and risk figures derived for the high volume/high exposure uses discussed in sections II.B and II.C. (3). Even in the case of high volume uses, with the exception of certain air blast application situations, exposure and risk are relatively low. Therefore, in the case of low volume/minor use situations exposure and risk is expected to be even lower than that of the high volume/high exposure uses. Because the Agency has determined that risk is acceptable (when protective clothing, etc., is used) in the high volume/high exposure uses it follows that risk would also be acceptable in the low volume/low exposure use patterns not analyzed in this Position Document if the same protective measures are required. Therefore, the Agency proposes to continue the registration of all uses not analyzed. The Agency points out, however, that all changes in use pattern practices identified in Section IV (e.g. protective clothing, respirators, etc.) shall apply to all minor uses not analyzed in this Position Document.

VI. Additional Testing Requirements

The Agency has identified several areas requiring additional testing. Registrants are hereby directed to submit such data as discussed below (FIFRA, 3(c)(2)(b)).

A. Oncogenicity

As discussed in sections II.A (1) and II.C (1) the evidence for oncogenicity is suggestive and warrants further study. Therefore, the Agency hereby directs registrants to conduct an oncogenicity bioassay using dimethoate in the same strains of mice and rats as that of the Gibel study. This study shall be completed and submitted within three years of the Agency's final determination (Position Document 4) concerning this chemical. Protocols for this study shall be submitted to the Agency within 3 months of the publication of the final Notice of Determination for dimethoate.

B. Mutagenicity

As discussed in section II. C (2) insufficient data exists upon which to base a mutagenicity risk assessment. The Agency concludes, therefore, that additional testing is required. The Agency hereby directs registrants to provide adequate test data concerning dimethoate's ability to cause gene mutations in animal cells. Registrants shall also conduct a dominant lethal study in mice as well as studies designed to detect spindle effects which may result in numerical chromosomal aberrations. Protocals for these studies shall be submitted to the Agency within 3 months of the publication of the final Notice of Determination for dimethoate. Tests shall be completed and submitted within eighteen months of the publication of the final Notice of Determination for dimethoate. In addition, further testing may be required based on the results of the studies discussed above in order to properly evaluate mutagenic potential and or risk.

C. Delayed Neurotoxicity

As discussed in Dimethoate Position Document 1 (EPA 1977) and in section II.A (4)(a) of this document, insufficient data is available to determine whether dimethoate can induce delayed neurotoxic effects. Therefore, the Agency hereby directs registrants to conduct appropriate neurotoxicity testing in accordance with the final registration guidelines. Protocols for these studies shall be submitted to the Agency within 3 months of the publication of the final Notice of Determination for dimethoate. These tests shall be completed and submitted within eighteen months of the promulgation of the final registration guidelines.

D. Applicator Exposure Data

As discussed in section IV.C (4) there is insufficient applicator exposure data concerning air blast application situations to determine whether there are sufficient margins of safety for reproductive/teratogenic effects. The Agency hereby directs registrants to conduct appropriate field studies to determine worker exposure (dermal and inhalation) during application of dimethoate using air blast type application equipment. Registrants shall gather such data for each crop where air blast equipment is used or on crops deemed representative of such applicator exposure situations. Registrants shall submit to EPA proposed test protocols for gathering applicator exposure data within three months of the Agency's final determination and shall complete all such tests and submit all exposure data within eighteen months of the Agency's final Notice of Determination concerning this chemical.

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*Copies of non-copyrighted references will be provided on request. There will be a charge to cover duplication costs for such requests. A copy of the Position Document and all references are available for inspection in the Special Pesticide Review Division (TS-791), Office of Pesticide Programs, Environmental Protection Agency, Crystal Mall 2, Room 717, 1921 Jefferson Davis Highway, Arlington, Virginia 22202.

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